St Lideta Health Science college

Department of Pharmacy

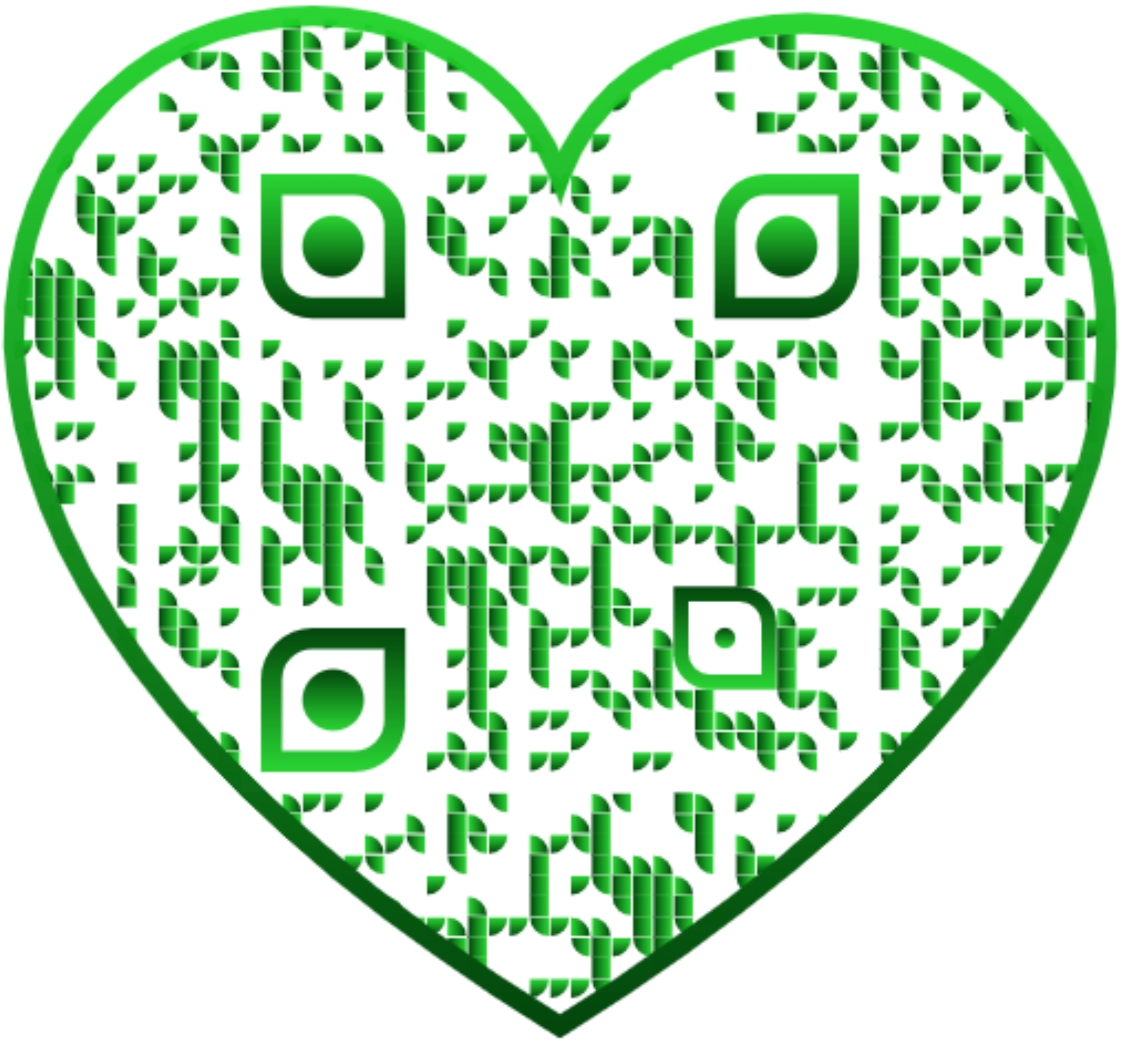
COURSE TITLE: IPP–II

- **Lecture note for clinical pharmacy degree students**
- **Credit hrs: 4**

INSTRUCTOR: TESFU NEGUSSIE

QUALIFICATION:

- **MPH**
- **MSC**
- **BA**
- **Bpharm**



A. Course synopsis

1. Semisolids
2. Suppository & Pessary
3. Micromertics
4. Powders & Granules as a dosage form
5. Diffusion & dissolution
6. kinetics and drug stability
7. Radiopharmaceuticals
8. Incompatibilities
9. Modified release dosage forms
10. Cosmetics

B. Teaching methodology

- Lecture
- Discussion

C. Assessment methods

- Assignment = 20%
- Mid-exam = 40%
- Final exam = 40%
- Total = 100%

D. References

1.P. J. Sinko, Martin's Physical Pharmacy and Pharmaceutical Sciences, 5th Edition, Lippincott Williams & Wilkins, Philadelphia, 2006.

2.M. J Wilson K, Pharmaceutical Compounding and Dispensing, Pharmaceutical press, 2006.

3.L. V Allen, N. G Popovich, H. C Ansel, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 8th edition, Lippincott Williams & Wilkins, 2004.

4.J. E Thompson and L.Davidow, a Practical Guide to Contemporary Pharmacy Practice, 2nd edition, Lippincott Williams & Wilkins, 2003.

5.A. Martin, J. Swarbrick and A. Cammarata, Physical Pharmacy, 3rd Edition, Lea & Febiger, Philadelphia, 1983.

6.A. T. Florence and D. Attwood, Physico-chemical Principles of Pharmacy, Macmillan Publishers Ltd., London, 1981

7.S. C. Wallwork and D. J. W. Grant, Physical Chemistry for Students of Pharmacy and Biology, 3rd Edition, Longman Group Ltd., London, 1977.

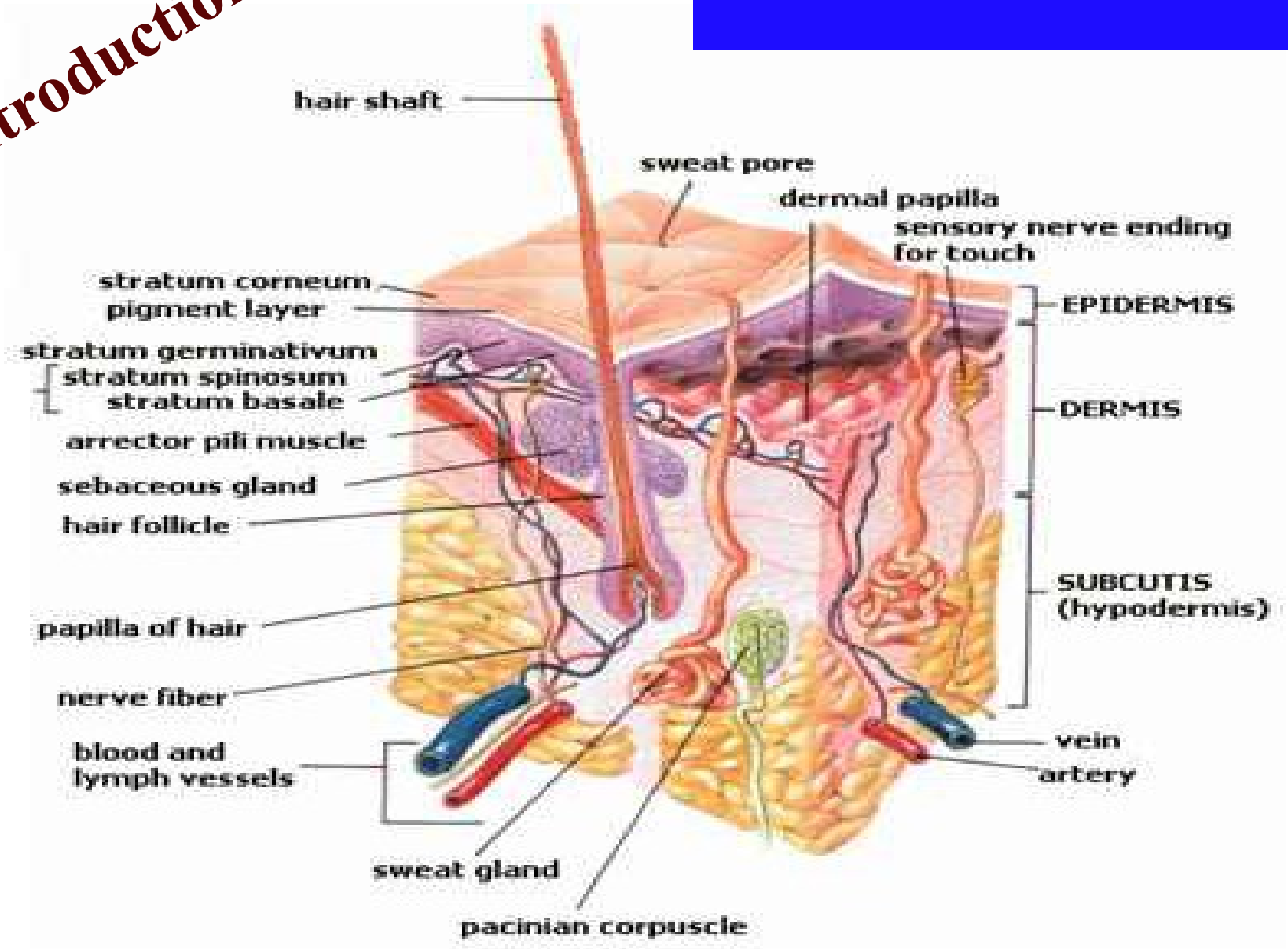
8.M. E. Aulton, Pharmaceutics: the science of dosage form design, 2nd ed., Churchill Livingstone, Edinburgh, 2002.

9.Hardee, G. E. and Baggot, J. D., Development and Formulation of Veterinary Dosage Forms, 2nd ed. Marcel Dekker, Inc. New York, 1998.

10.Breuer, M. M., Cosmetic Science, Academic Press, London, 1978.

Introduction

Physiology and anatomy of skin



The human skin comprises three tissue layers:

1. Epidermis [hypodermis]

- Has stratified squamous keratinizing epithelium with no blood vessels, and is nourished by **diffusion** from the dermis

➢ **Stratum corneum** is the outermost layer of epidermis

2. Dermis: consists of matrix of connective tissue, nerves, blood vessels and lymphatic

3. Subcutaneous fat : Consists of connective tissue , blood vessels and nerves

Function of the skin

➢ Protection

➢ Sensation

➢ Heat regulation

➢ Excretion

Rational approach to drug delivery & via the skin

There are three main ways to attack the problem of formulating a successful topical dosage form:

1.Manipulate the barrier function of the skin

2.Direct drugs to the viable skin tissues without using oral, systemic or other routes of therapy

3.Use skin delivery for systemic treatment [Transdermal Drug Delivery]

Factors that influence transdermal delivery [Subcutaneous drug absorption]

- After applying preparation to diseased skin, the clinical result arises from the following sequence of processes:
  1. Release of the medicament from the vehicle
  2. Penetration of dug through the skin barriers
  3. Activation of the pharmacological response
- Effective therapy optimizes these steps as they are affected by three components: drug, vehicle and skin
- Thus factors affecting subcutaneous drug absorption can be categorized as biological and physicochemical factors

1. Biological factors

- **Skin condition** : Intact, healthy skin is a tough barrier while inflamed /damaged skin has defective stratum corneum, hence has improved permeability
- **Skin age:** Skin of young is more permeable than that of elderly
- **Regional skin sites:** Better drug absorption from thin skin such as scrotum than from thick skin region such as palm and foot
- **Blood flow**: Increased blood flow enhances transdermal absorption

2. Physicochemical factors

Skin hydration

- When water saturates the skin the tissue swells, softens and wrinkles and its permeability & hence drug penetration increases markedly.

Temperature

- Penetration rate of drug through human skin changes tenfold for a large temperature variation

Reason: Diffusion coefficient increases as temperature increases

Molecular size

- Absorption is inversely related to molecular weight: small molecules penetrate faster than large ones

Methods of enhancing drug penetration via the skin

Hydration *:* Increases penetration rate of most substances via stratum corneum

Reason: Water opens up the compact layer of the stratum corneum or the horny layer

Note:

Moisturizing factors, occlusive films, hydrophobic ointments & transdermal patches all enhance skin bioavailability of drug

Dermatological products

- They are disperse systems designed for application topically to the skin or mucous membrane lining accessible body cavities such as the eye, nose, ear, vagina, rectum, buccal tissue, or the urethral membrane either for local or systemic effects.
- In general, topical dermatological products are designed to deliver drug into the skin for treating dermal disorders.
- The major classes of agents that are used topically include corticosteroids, antifungals, acne products, antibiotics, emollients, antiseptics and local anaesthetics.

Types of dermatological products

- Ointments
- Pastes
- Creams
- Gels

Semisolids

- Lotions
- Liniments
- Collodions
- Solutions
- W/O emulsions

Topical Liquid dosage forms

Pharmaceutical ointments and pastes

- Pharmaceutical ointments are semisolid systems
- Applied externally to the skin and to mucous membranes, e.g. the rectum, the vagina/vulva, the eye.

Types [2]

- **Medicated ointments** :used for the treatment of infection, inflammation and pruritus.
- **Non-medicated ointments** :used as emollient/lubricant

Pharmaceutical pastes

- Composed of ointment bases, gelatin, tragacanth, PEG, starch, pectin, or cellulose derivatives.
- Contain high concentration (>50% w/w) of dispersed fine powder such as starch, gelatin than ointment
- They are more viscous/stiff than pharmaceutical ointments, hence, paste never spread readily over the skin's surfaces, thus pastes of corrosive anti-psoriatic drugs never spread to cause irritation to healthy skin
- Pastes that contain hydrophilic components are used on traumatized oozing surfaces while Pastes having hydrophobic components are water impermeable and hence , prevent dehydration of application site

Note:

- Formulation of ointments and pastes involves dispersal or dissolution of selected drug into ointment base
- Physicochemical properties of both the drug & ointment base affect the clinical and non-clinical performance of semisolid dosage forms

Ointments

- Ointments are semisolid preparations intended for external application to benefit from their clinical and non-clinical performances such as:
  - ❖**emollients**
  - ❖**protective skin barriers**
  - ❖**vehicles for medications**
  - ❖ **treatment**

Ointment Bases

- Hydrocarbon Bases
- Absorption Bases
- Emulsion/Water-miscible/removable bases
- Water-soluble Bases

Qualities of an Ideal Ointment Base

- Compatible with the skin
- Stable during shelf-life
- Smooth and pliable
- Nonirritating, non-sensitizing [grittiness]
- Inert
- Easily release incorporated medication

Hydrocarbon Bases (Oleaginous Bases)

- Anhydrous and insoluble in water
- Contain no water
- Absorbs less than 5% water under normal conditions
- Not washable
- Difficult to apply to (spread over) wet surfaces (mucous membranes, wet skin)

  Examples: Petrolatum USP, White Petrolatum USP, Yellow & White Ointments

Properties of Hydrocarbon Bases (Oleaginous Bases)

- Emollient
- Occlusive
- Non-water washable
- Predominantly hydrophobic
- Greasy
- Anhydrous (ideal for hydrolyzable antibiotics)
- Chemically inert

Hydrocarbon bases

- Petrolatum (semisolid hydrocarbon or hard paraffin) melting point 38-68 °C, yellow to light amber)
- White petrolatum (not water washable, occlusive)
- Yellow ointment (95% petrolatum + 5% yellow wax)
- Mineral oil (liquid petrolatum) is used as a levigating agent to incorporate lipophilic solids into ointments

Microcrystalline wax

- Solid mixture of linear & saturated alkanes
- Used to enhance viscosity of ointments (and creams).
- Provides greater physical stability to formulations containing liquid paraffin by reducing its bleeding

Absorption Bases [Non-emulsified bases & Water in oil emulsions]

- Hydrophobic with added surface-active agents

Properties

1. Absorb water
2. Anhydrous
3. Water insoluble
4. Not-washable
5. Permits inclusion of water insoluble medication

Examples: Wool fat, Hydrophilic petrolatum

1. Hydrophilic petrolatum USP (anhydrous absorption base) (Components:cholesterol, stearyl alcohol, white wax, white petrolatum)

Procedure:

- Melt stearyl alcohol & white wax together on a steam bath, then add cholesterol to the melt & stir until it completely dissolves
- Add white petrolatum and mix
- Remove from water bath & stir until mixture get congealed

2. Aquaphor : Refined hydrophilic petrolatum, takes up three times of water per weight

Examples of Absorption Bases

A. Simple ointment BP — Master formula (g)

1. Wool fat [Lanolin] …… 50
2. Hard paraffin…… 50
3. Cetostearyl alcohol…… 50
4. Yellow or White soft paraffin … 850

Note:

- Lanolin can absorb twice its own weight of water
- It is self-emulsifying, producing stable w/o emulsions
- It is used to prevent drying and chapping of the skin

B. Emulsifying ointment BP Master formula

- Emulsifying soft wax …… 300 g
- White or yellow soft paraffin …… 500 g
- Liquid paraffin …… 200 g

Note :

Weigh both Emulsifying soft wax and soft paraffin using waxed paper to allow their full recovery during transfer to evaporating dish for melting.

Absorption bases [water- in-oil emulsions]

- Permit incorporation of aqueous solutions
- Prepared by incorporating hydrous lanolin[a mixture of lanolin & 25–30% water into paraffin oil]

e.g. **Oily Cream BP** is a water in oil emulsion ointment base composed of wool alcohols (50% w/w) and water (50% w/w).

Water-miscible/removable bases

- Used to form oil in water emulsions
- Contain both water soluble and insoluble components

Advantages

- Able to accommodate large volumes of water

  E.g. aqueous solutions of drug, or excess exudates from abrasions and wounds can be taken-up

- Not occlusive
- Easily washed from skin and from clothing
- Readily applied to (and removed from) hair
- Aesthetically pleasing

Types of water-miscible/ removable bases:

1. Emulsifying ointment bases
2. Cetrimide emulsifying ointment bases
3. Cetomacrogol emulsifying ointment bases

Note :

- Each of these bases contains liquid paraffin ,soft paraffin and emulsifying wax
- The most important component of this ointment base is emulsifying wax
- Classification of water-miscible base is based on the type of incorporated **emulsifying wax**

Types of emulsifying waxes

- Anionic emulsifying wax
- Cationic emulsifying wax [Cetrimide Emulsifying Wax]
- Non-ionic emulsifying wax [Cetomacrogol Emulsifying Wax]

Anionic emulsifying wax

Example :

1. Aqueous Cream BP

- Cetostearyl alcohol …… 90 g
- **Sodium lauryl sulphate ……**10 g
- Purified water …… 4 ml

2. Hydrophilic ointment, USP Master formula(% w/w)

i. Stearyl alcohol ……25.000
ii. White petrolatum ……25.000
iii. Methylparaben ……0.025
iv. Propylparaben ……0.015
v. Sodium lauryl sulfate …… …1.000
vi. Propylene glycol ……..12.000
vii. Purified water ……..37.000

Note:

Stearyl Alcohol: Hydrophobic oil soluble component, used as an emollient, emulsifier and thickener

Propylene glycol : Hydrophilic viscous liquid used in the aqueous phase to increase viscosity

Sodium lauryl sulfate :Surfactant/emulsifier

Cationic emulsifying wax [*Cetrimide emulsifying wax, BP]*

- Cetostearyl alcohol ……..……..900 g
- Cetrimide …… 100 g

Non-ionic emulsifying wax [Cetomacrogol emulsifying Wax, BP]

- Cetostearyl alcohol……800 g
- Cetomacrogol 1000 ……200 g

Water-soluble (water-washable or "greaseless") bases

- Composed entirely of water-soluble ingredients
- Known as greaseless due to lack of oleaginous materials.
- Absorb water to the point of solubility.
- Water-soluble bases are made of carbowax or polyethylene glycol (PEG) as the base.
- They are oil/lipid free and non/less occlusive.
- Difficult to incorporate aqueous solutions because they soften greatly with the addition of water.
- Better used for incorporation of nonaqueous or solid substances

- Polyethylene glycol (PEG) make up majority of components of the water-soluble base
- PEG is a polymer of ethylene oxide and water represented by the formula :

$$OHCH_2\ (CH_2OCH_2)n\ CH_2OH.$$

- PEG with a Mol. Wt . <1000 are liquid while with Mol. Wt > 1000 are solid at room temp & equal to 1000 have soft consistency[Semisolid]
- Blends of high & low-molecular-weight PEG forms Ointment base with better consistency

Polyethylene glycol ointment, NF :

A. Base with low (<5% w/w) water incorporation capacity)

Formulation ingredient (% w/w)

- Polyethylene glycol 4000 ……40
- Polyethylene glycol 400 ……..60

Procedure:

- Heat the two ingredients in a water bath to 65 0C.
- Allow to cool and stir until congealed

B: Base with low (>5% w/w) water incorporation capacity)

Incorporate up to 6-25% of an aqueous solution or water if a portion of lower Mol.wt PEG is replaced with stearyl alcohol

- PEG 4000 ……..40 % w/w
- PEG 400……. ……55 % w/w
- Stearyl alcohol….. …… 5 % w/w

- Another water-soluble base is the ointment prepared with propylene glycol and ethanol, which form a clear gel when mixed with 2% w/w hydroxypropyl cellulose (HPC)
- It is commonly used as a dermatologic vehicle.

Advantage of water-soluble bases

- Easily removed by washing; do not stain sheets or clothes.
- Non-occlusive
- Do not support microbial growth
- Compatible with majority of therapeutic agents.
- Miscible with exudates from inflamed sites.

Disadvantages of water-soluble bases

- Reacts with plastic containers
- Incompatible with some drugs

Example:

- Phenol
- Iodine
- bacitracin,
- Penicillin
- Quaternary ammonium compounds

Factors to be consider during selection of appropriate base

1. Desired release rate of the drug
2. Desirability of topical use or percutaneous drug absorption [Transdermal drug delivery]
3. Desirability of exclusion of moisture from the skin
4. Desirability of retention of moisture onto the skin
5. Solubility of the drug in the ointment base
6. Effect of the drug to the ointment base
7. Requirement that the ointment base is easily removed by washing with water
8. Characteristics of the surface to which the base is applied

Summary

Ingredients used in ointment preparation

- Drug
- Base [or vehicle]
- Additives
  - Preservatives
  - Antioxidants

Preservatives

- Ointments containing water requires preservative
- Ensure proper partitioning of MIC of antimicrobial species is within the aqueous phase.

Examples

- Phenolics: phenol (0.2–0.5%), chlorocresol (0.075–0.12%)
- Benzoic acid and salts (0.1–0.3%)
- Methylparabens (0.02–0.3%)
- Propylparabens (0.02–0.3%)
- Benzyl alcohol (3.0%)
- Phenoxyethanol (0.5–1.0%)

Antioxidants: Employed to prevent or reduce oxidation of either the non-aqueous components of the ointment base (e.g. mineral/vegetable oils) &/or therapeutic agent.

- **Lipophilic antioxidants** (dissolve within non-aqueous vehicle) ,Examples :
    - Butylated hydroxyanisole (0.005–0.02%),
    - Butylated hydroxytoluene (0.007–0.1%),
    - Propyl gallate (1%)
- **Hydrophilic antioxidants** (Dissolve in aqueous phase)

Examples:

- Sodium metabisulphate (0.01–0.1%)
- Sodium sulphite (0.1%)

Ophthalmic ointment

- Must be sterile
- Each Ingredient must be:
  - separately sterilized under rigid aseptic conditions
  - Weighed/measured under aseptic techniques during manufacturing processes

Note:

- Terminal sterilization of ophthalmic ointment is difficult to perform

Ingredients of ophthalmic ointment

- Mixtures of mineral oil & white petrolatum
- Aqueous solution or finely micronized drug powder
- Antimicrobial preservatives :
  - Methylparaben (0.05%)
  - Propylparaben (0.01%)
  - Phenylmercuric acetate (0.0008%)
  - Chlorobutanol (0.5%)
  - Benzalkonium chloride (0.008%)

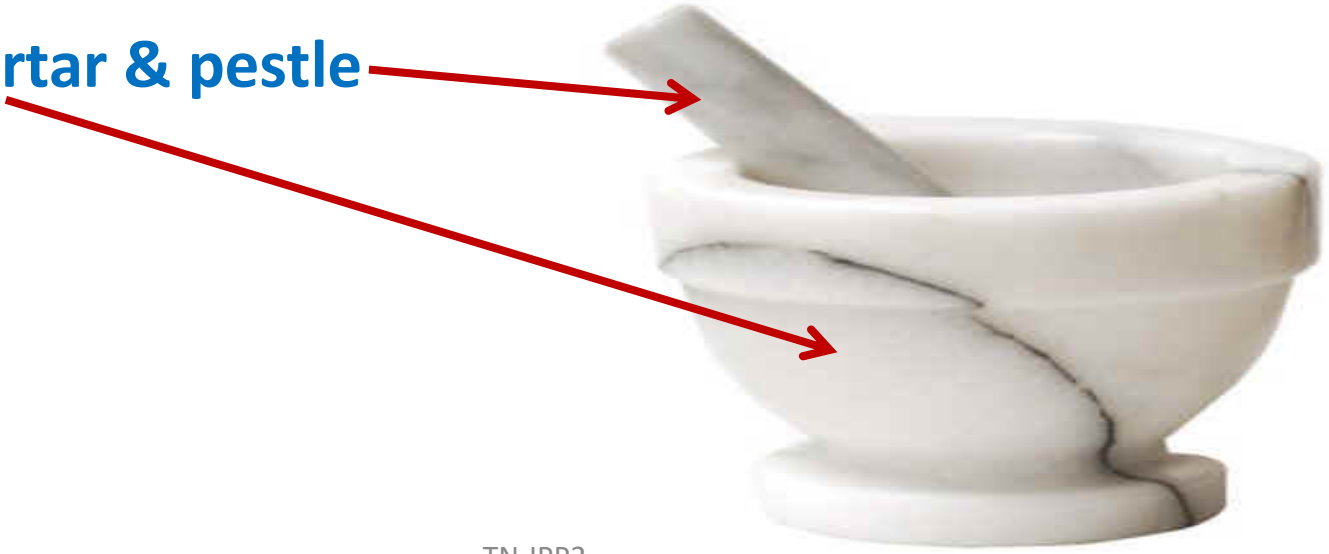
Qualities of ophthalmic ointment base

- Have ability to diffuse medication throughout the secretions bathing the eye
- Non-irritating to the eye
- Freedom from gritty particles
- have a softening point close to body temperature, both for patient comfort and for drug release
- Sterile

Instruments used for Ointment Preparation

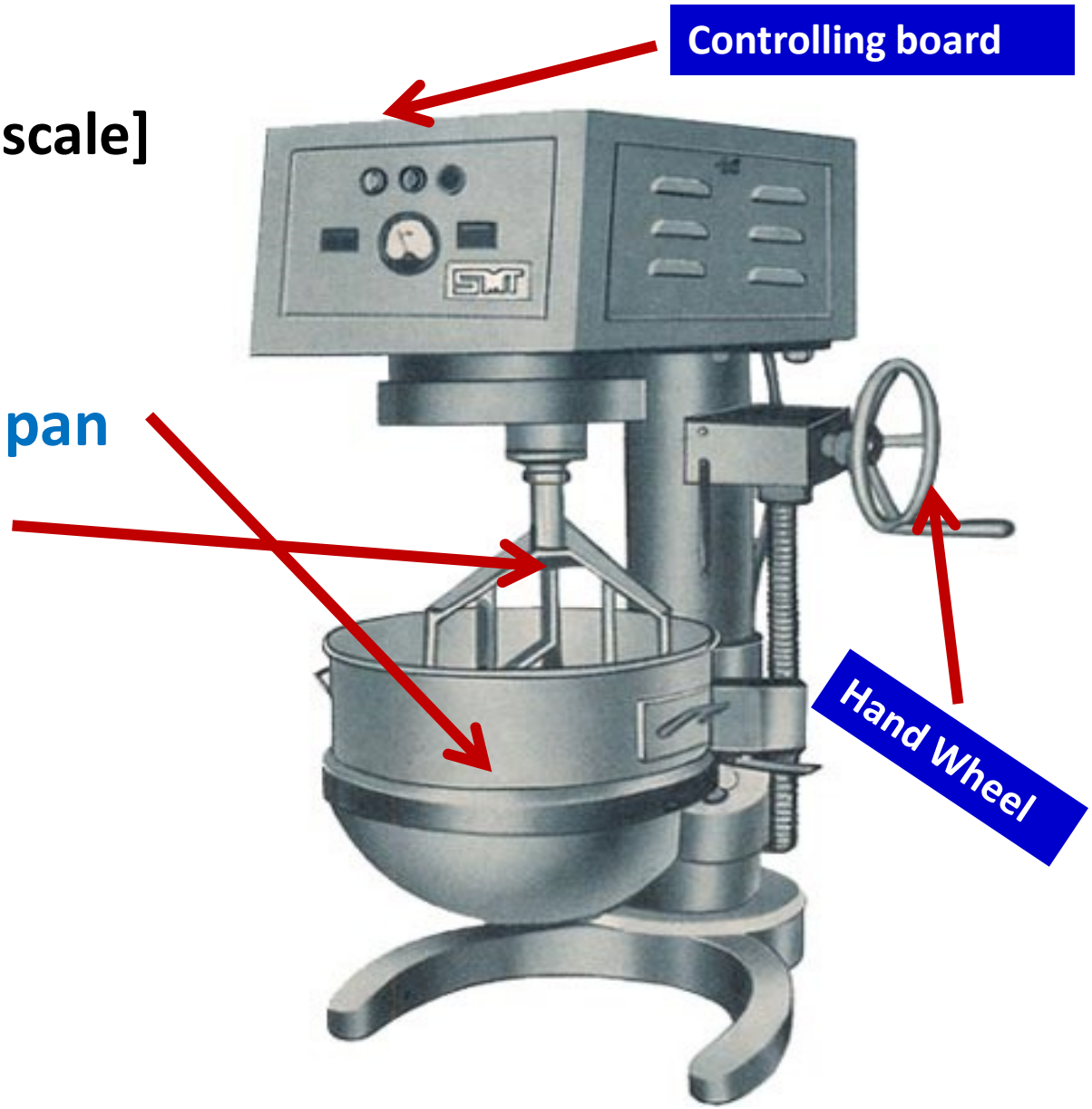
Small scale [Laboratory scale]

- Balance
- Sieve
- Evaporating dish (basin)
- Water bath
- Ointment slab (tile) & spatula **or**
- Mortar & pestle



Large scale [Industry scale]

1. Balance
2. Sifter
3. Jacketed melting pan
4. Ointment mixer
5. Homogenizer
6. Filling machine



Ointment Preparation Methods

A. Incorporation by levigation or trituration

1. Use of stainless steel spatula with a long, broad, flexible blade or rubber spatula
2. Ingredients should be finely powdered on a mortar and pestle
3. Use of levigating agents e.g. mineral oil and glycerin
4. Water soluble salts are incorporated in the smallest possible amount of water.

B. Fusion Method

- Involves melting components (paraffin, stearyl alcohol, white wax, yellow wax, and high molecular weight PEGs) together to form a homogeneous solution.
- Used when the base contains solids that have higher melting points (e.g., waxes, cetyl alcohol, or glyceryl monostearate).

In general:

1. Melt oil phase separately starting with the materials having highest melting point on water bath
2. Heat ingredients in the water phase separately at temperature higher or equal to the oil phase
3. Combine the two-phases and mix
4. Add the volatile materials after cooling the mixture to 40° C or less

Compound Benzoic Acid ointment[Whitefield's ointment]

Ingredients	**Master formula(g)**
Benzoic acid in fine powder	60
Salicylic acid in fine powder	30
Emulsifying wax	300
White soft paraffin	500
Liquid paraffin	200

Use: Antifungal

Calamine Ointment NF

Formula	**Quantity**
Calamine	170 g
Anhydrous lanolin	40 g
Yellow wax	40 g
Petrolatum	750 g

Use: Protective and astringent dressing

Bacitracin Ointment USP

Formula

Bacitracin	500,000 units
Mineral oil	65 g
White Petrolatum	925 g

	1,000 g

Bacitracin Ointment USP

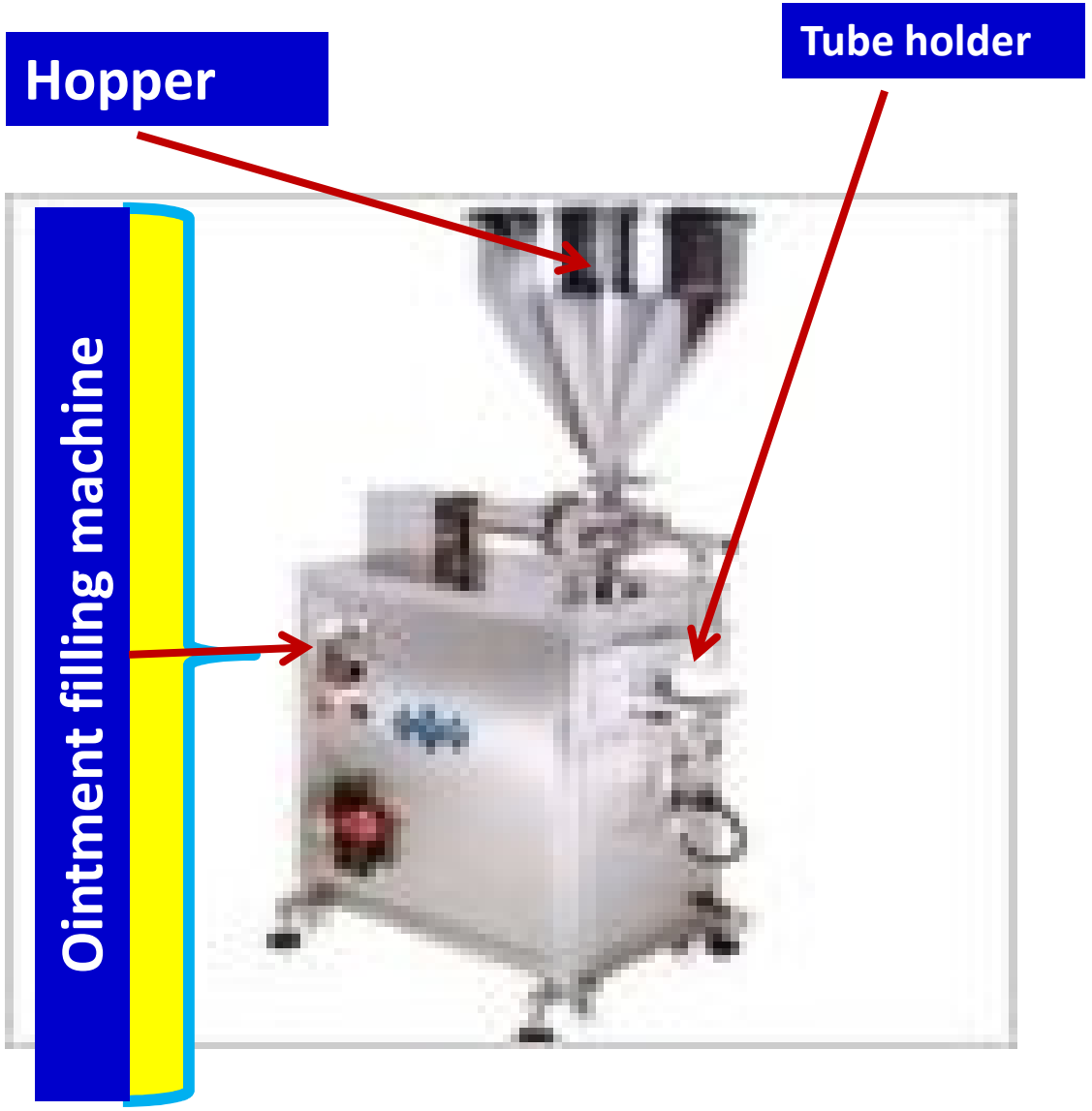
Preparation- Mechanical incorporation. Replacement of up to 40 g of mineral oil by an equal amount of white petrolatum will give a firmer preparation

Packaging Semisolid Preparations

- Topical dermatologic products are packaged in jars or tubes
- Ophthalmic, nasal ,vaginal and rectal semisolids are always packaged in tubes

Filling Ointment Jars and Tubes

- Manually as in small scale preparation
- Automated , filling ,closing , crimping and labeling for large scale tube packaging


Hopper
Tube holder
Ointment filling machine

Compendia Requirements

- ❖ Microbial Content must meet acceptable standards
- ❖ Preparations prone to microbial growth must contain antimicrobial preservatives
- ❖ Topical preparations need not be sterile except ophthalmic preparations
- ❖ Microbial limits are set for certain articles in the USP

Example

- Betamethasone Valeroate Ointment *should fulfill* tests for the absence of *Pseudomonas aeruginosa and Staphylococcus aureus*

Minimum Fill

- The USP's minimum fill test involves determination of the net weight or volume of the contents of filled containers to ensure proper contents against label claim

Packaging , Storage and Labeling

- Packaged either in large mouth ointment jars or metal or plastic tubes.
- Light sensitive preparations are packaged in opaque or light-resistant containers
- Stored in well-closed containers in a cool place to protect against product separation.
- The labeling for certain ointments and creams include the type of base used e.g. water soluble or water insoluble.

Pharmaceutical creams

- are basically ointments which are made less greasy by incorporation of water

or

- are viscous semi-solid emulsions for external use.

Functions of cream

- protective
- therapeutic
- prophylactic
- Emollient without occlusive effect

Types of cream

- Medicated or non-medicated cream
- 'water-in-oil'[cold cream] or 'oil-in-water' [Vanishing cream] depending on emulsifying agent used
- Features of Hydrophilic creams [vanishing cream]
  - Upon rubbing onto skin, evaporation of the external aqueous phase increases conc. of water-soluble drug in the oily film that adheres to skin
  - This increase in drug concentration gradient across the stratum corneum promotes percutaneous absorption over the absorption site

- Creams based on w/o emulsions, such as cold cream, are useful as softening and cleansing agents.
- The name, cold cream, refers to the cooling sensation associated with the slow evaporation of the dispersed aqueous phase
- The use of creams as drug delivery systems is associated with good patient acceptance.

- ❖ Drug incorporation into a cream needs that the drug :
  - ➢ be soluble in sufficient concentration
  - ➢ have relatively wide therapeutic window since accurate dosing is difficult
  - ➢ not crystallize upon evaporation of water
- ❖ Creams are preferred to ointments

Reasons

- Easy removable from its container
- High spreadability

Water-in-oil cream formulation (HLB 12)

Example-1

- **Part A**
  - Mineral oil ……..50.0 (% w/w)
  - White wax ……..15.0 (% w/w)
  - Sorbitan monostearate ….. 2.0 (% w/w)
- **Part B**
  - POE- sorbitan monostearate …3.0 (% w/w)
  - Water, q.s. ……..30.0 (% w/w)

Procedure:

- Part A is heated at 70 ^{0}C until completely melted.
- Part B is added at 70 ^{0}C, mixed and then cooled to room temperature

Oil-in-water cream formulation HLB 13

Example-2

- **Part A**
  - **Stearic acid ……10.0 (% w/w)**
  - **Mineral oil ……..8.0 (% w/w)**
  - **White petrolatum …… 6.0 (% w/w)**
  - **Sorbitan monostearate …….2.0 (% w/w)**
- **Part B**
  - **POE- sorbitan monostearate ……1.0 (% w/w)**
  - **Water ……..73.0 (% w/w)**
  - **Preservative ……Q.S.**

Procedure

- **Same as example-1, above**

Pharmaceutical gels and Jellies

- Gels are semisolid systems consisting of dispersions of small or large molecules in aqueous or liquid vehicle
- Rendered jelly like by addition of gelling agent
- Gels are sometimes called jellies
- Gels may thicken on standing forming a thixotrope , and must be shaken before use to liquefy the gel and enable pouring

Components of gels

- Drug substance [if it is medicated gel]
- Alcohol and/or propylene glycol
- Antimicrobial preservatives [parabens or chlorhexidine gluconate]
- Stabilizers such as disodium edetate
- Water
- Gelling agents

Examples of gelling agents

- Poloxamer
- Alginic Acid
- Carbomer
- Colloidal Silicon Dioxide
- Alginate
- Tragacanth
- HPMC
- HEC
- Calcium CMC
- Bentonite
- MC
- Sodium
- Povidone
- HPC
- Sodium CMC

Physical properties of gels

- ❖ Imbibitions
- ❖ Swelling
- ❖ Syneresis
- ❖ Ageing
- ❖ Thixotropy
- ❖ Vapor adsorption

Imbibition :uptake of water or other liquids without any considerable increase in its volume.

Swelling : Increase in the volume of gel by uptake of water or other liquids.

Influenced by temperature, pH, presence of electrolytes, and other formulation ingredients.

Syneresis : contraction or shrinkage of gels as a result of squeezing out of dispersion medium from the gel matrix. If it occurs, then the original gel is thermodynamically unstable

Ageing: Slow aggregation of colloidal substances of the gel resulting in the formation of denser networks of gelling agents

Thixotropy *:* Reversible gel - to – sol formation with no change in volume or temperature of the gel

Vapor adsorption: The solid mass (xerogel) formed by removal of water via evaporation or freeze drying adsorbs vapor due to its porous nature & large surface area

Classification of gels

1. Based on the solvent phase of the gels

- ❖Hydrogels
- ❖ Organogels

Hydrogels & organogels contain water & organic liquid as the main continuous phase solvent, respectively.

Hydrogels contain significant amounts of water, but remain water insoluble

2. Based on gelling agent

- Inorganic gels
- Organic gels

Inorganic gels use precipitates of inorganic salts, such as magnesium hydroxide, aluminum hydroxide or bentonite as gelling agents, while organic gels use a carbon-based hydrophilic polymer.

Inorganic gels are usually two-phase systems, whereas organic gels are generally single-phase systems.

3. Based on flow characteristics

- Shear thinning (pseudo-plastic) gels
  - Viscosity decreases & flow increases on agitation
- Shear thickening (dilatant) gels
  - Viscosity increases and flow decreases on agitation
- Thixotropic gels
  - Viscosity decreases & flow increases over time under same agitation rate

    Example: Inorganic gels
  - Display higher viscosity & a semisolid state on standing & become low viscosity liquids on agitation

Drug release from the gel

The diffusion rate of a drug from a gel depends on:

- physical structure of polymer network and its chemical nature
- Level of gel hydration
  - If the gel is highly hydrated, diffusion occurs through the pores
  - In gels of lower hydration, the drug dissolves in the polymer and is transported between the chains
- Polymer cross-linking increases the hydrophobicity of a gel and reduces diffusion rate of the drug

Hydrogels : Prepared with water - soluble materials or water - dispersible colloids

Materials used with water to form hydrogels

- **Natural & synthetic gums** such as tragacanth, sodium alginate, and pectin
- **Inorganic materials** such as alumina, bentonite, silica, and veegum
- **Organic materials** such as cellulose polymers

Note: These materials either be dispersed as fine colloidal particles in aqueous phase or completely dissolve in water to gain gel structure

- With the advancement in polymer science, hydrogel-based systems that respond to specific biological or external stimuli like pH, temperature, ionic strength, enzymes, antigens, light, magnetic field, ultrasound, and electric current are being designed and evaluated as smart delivery systems for various applications

Stimuli - Responsive Hydrogels

- Change their swelling pattern in response to pH, temperature & ionic strength of the swelling medium
- Such response to stimuli makes them very attractive for drug delivery & biomedical applications.

Types:

- **pH-responsive hydrogels**
- **Thermo-responsive hydrogels**
- **Ionic-responsive hydrogels**

pH-responsive hydrogels

- Polymers containing carboxylic acid or amine-pendant groups show pH - dependent swelling and gelling[i.e., phase transition] characteristics in aqueous media
- Ionic strength of surrounding fluids significantly influences equilibrium swelling of pH- responsive polymers.
- Higher ionic strength favours gel-counter ionic interactions & reduces osmotic swelling forces

Examples:

1.Methacrylic acids (e.g., carbomers) undergo a gel-to-sol transition at lower pH and a sol-to-gel transition when pH is increased

Reason: The degree of ionization of acidic carboxylic groups increase at higher pH triggering electrostatic repulsions b/n chains & increased hydrophilicity & swelling

2. Polymers that contain amine-pendant groups **swell** at lower pH environment due to ionization & repulsion b/n polymer chains [sol-to-gel transition] & involve gel-to -sol transition at higher pH

Thermo-responsive Hydrogels

- Exists as solution at room temperature and transforms into gel on instillation into a body cavity

Advantage: Such transition

- ❖Improves drug administration mode
- ❖Help in modulating the drug release

Example

- Triblock copolymer PLGA – PEG – PLGA, undergoes sol - to - gel transition **on intra-tumoral injection**, and releases **paclitaxel** for six weeks

Ionic-Responsive Hydrogels

- Administration of **sodium alginate aqueous eye drops** show **sol –to-gel conversions** in the eye due to its interaction with cations in the tear fluid

Result:????

Factors affecting strength of gel structure of hydrogels

- Quantity of gelling agent
- Nature of gelling agent
- Molecular weight of gelling agent
- Product pH
- Gelling temperature[gel point]

- Gel pt. for gelatin is 30 °C, Thus, gelatine form gel at 30 °C but not above or below
- Gel pt. for Methyl Cellulose is > 50 ° C
- MC form no gel below 50°C as it get dissolved.

Jellies

- Clear and uniform semisolid gels of hydrophilic polymers, in which the structurally coherent matrix contains a high proportion of liquid, usually water.
- Commonly formed by adding a thickening agent, to an aqueous solution of a drug substance.
- The thickening agent could be natural gums, such as alginates, tragacanth & pectin; or synthetic derivatives of natural substances Na-CMC and MC
- Jellies, being aqueous, are prone to bacterial growth. Thus, antimicrobials are usually added as preservatives

Unit 2: Rectal and Vaginal Dosage Forms
[Suppository & Pessary]

Physiology of the rectum

Main rectal physiological features related to rectal drug delivery and hence to the formulation :

1. **Rectal wall** is composed of one cell thick epithelial layer with no villi (or microvilli)
2. **Mucus content:** Empty rectum contains ≈ 3 ml of mucus, that spread over its surface area of ≈ 300 cm^2

Note: Fate of absorbable drug depends on the area of the rectum from which absorption has occurred

3. **Rectal pH** is essentially neutral with minimal buffering capacity.

- Thus,
    - rectal fluid is unable to alter degree of drug ionization
    - Salt forms of the drug determine local efficacy and/or systemic efficacy.

4. **Faecal matter** markedly affect both drug dissolution in the rectal fluids and subsequent systemic absorption

5. **Haemorrhoidal veins**: They are three in №.

- ❖ Upper (superior) haemorrhoidal vein (H.V)
- ❖ Middle haemorrhoidal veins
- ❖ Lower [inferior] haemorrhoidal veins

Where do they drain?

Note:

- Drug absorption into the lower and middle H.V by pass hepatic first pass effect since it enter systemic circulation via inferior vena cava and has no direct exposure to and hence metabolism by the liver.
- Drug absorbed into upper H.V conveyed to the liver via portal vein ,hence subjected to first-pass effect

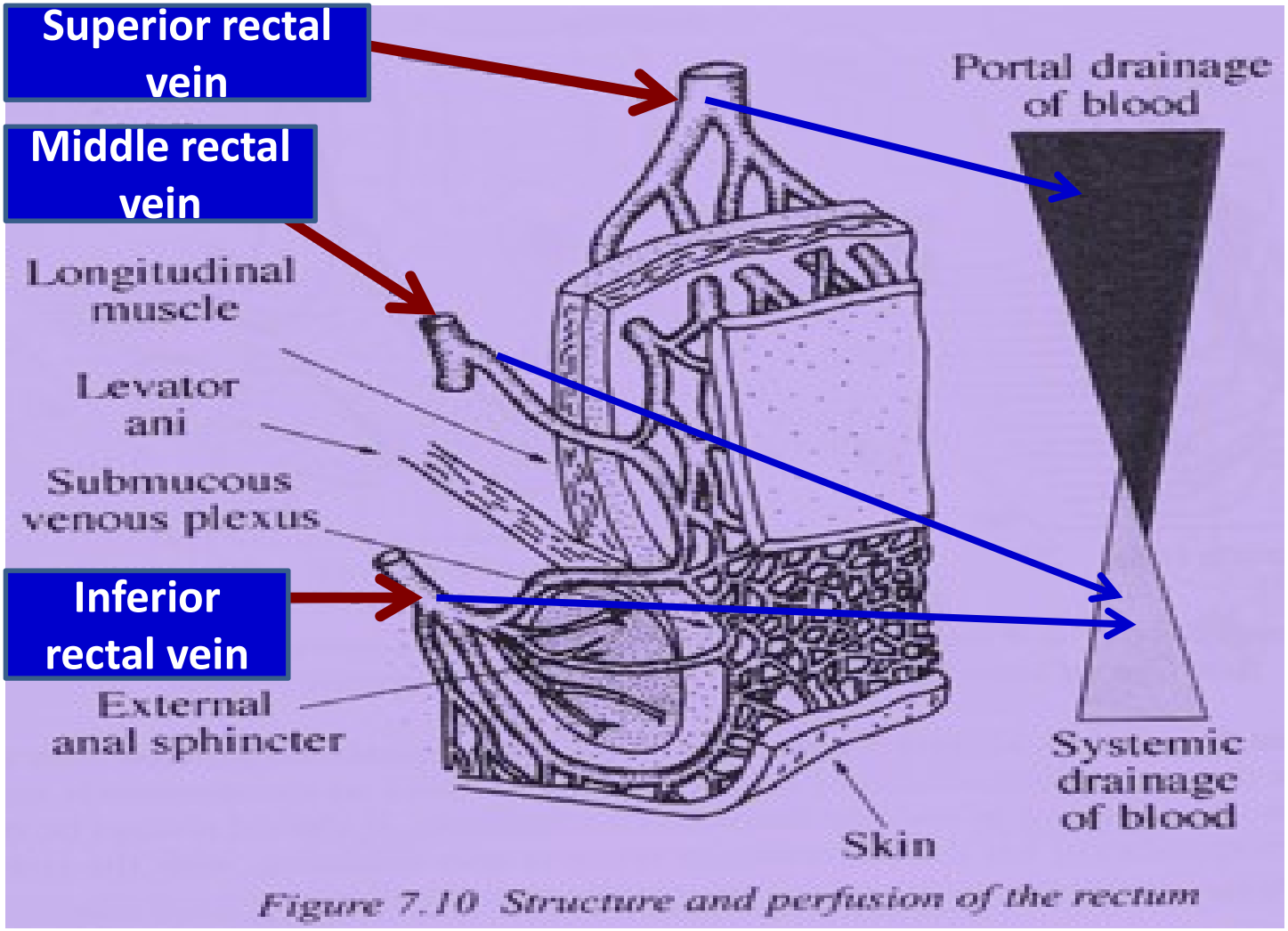


Figure 7.10 Structure and perfusion of the rectum

Examples of classes of drugs administered by rectal route for systemic absorption:

- Antiemetics (e.g. prochlorperazine)
- Antibiotics
- Anaesthetics
- Analgesics (e.g. oxymorphone-HCl)
- Anti-inflammatory agents
  (e.g. indometacin ,diclofenac-Na)
- Ergot alkaloids.

Note:

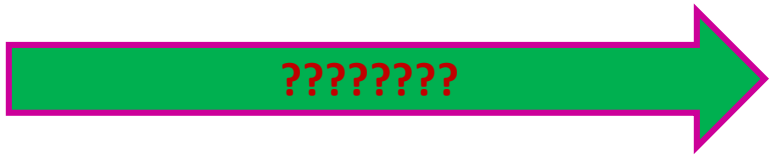
No esterase or peptidase in the rectal fluid …????

Rectal systemic drug absorption involves:

- **Melting /dissolution** of dosage form in rectal fluids
- **Diffusion** of the drug through the rectal fluid to reach rectal mucosa
- **Absorption** of drug through the rectal mucosa into systemic circulation

Note

- Various factors affect rate and extent of rectal drug absorption.



Formulation factors affecting rectal drug absorption

- Particle size of dispersed active agent
- Partition coefficient of therapeutic agent
- Degree of ionization of therapeutic agent
- Physicochemical properties of formulation base
- Site of absorption within the rectum

Physiological factors affecting rectal drug absorption

- Quantity of rectal fluid available
- Properties of rectal mucus
- Contents of the rectum
- Motility of the rectal wall

Formulation of rectal dosage forms

- Suppositories
- Semisolids
- Solutions
- Suspensions
- Emulsions
- Powder & tablets for rectal solutions & suspensions

Note: Suppositories are the most commonly used rectal d.f

Advantages of rectal dosage forms

1. Local treatment of infection and inflammation!
    - Haemorrhoids
    - Prostitis
    - Crohn's disease
    - Ulcerative colitis
2. Relieve constipation: eg: Glycerine suppository
3. Promote bowel evacuation via rectal irritation
4. Cleanse the bowel prior to surgery [intensive № 2].

5. Systemic treatment where oral drug absorption is not recommended
6. To administer drugs that are:
    - prone to degradation in the stomach
    - erratically absorbed from the upper git
    - extensively labile to first-pass metabolism

Disadvantages

1. Slow rectal drug absorption
2. High intra-subject and inter-subject variability
3. BA of drugs are affected by rectal content
4. Therapeutic agents may induce proctitis

Suppositories

Introduction

- Solid-dosage forms inserted into rectum , vagina or urethra
- Undergo softening, melting or dissolution to liberate therapeutic agent at site of application.
- Location of suppository within the rectum directly affects drug bioavailability
- Suppository formulation directly affects onset & duration of action of therapeutic agents

Suppository formulation	=	Drug + Base + Additive

Pictorial presentation of Suppository mould & Suppository

Types of Suppositories

1. Rectal suppositories

   Usually cylindrical or tapered to a point forming a bullet-like shape. Suppositories for adults weighs approximately 4 g and less for infants and children

2. Vaginal suppositories (pessaries)

   Globular, conical or oviform shape & weigh 5 g

3. Urethral suppositories (bougies)

   - Long and tapered (slender and pencil-shaped)
   - 60 mm long and 4-5 mm in diameter
   - Used for local anti-infective effects

Criteria for Satisfactory Suppository Base

- **Remain firm at room temperature** to allow insertion
- Should not soften below 30 ^{o}C to avoid melting during storage
- Have a narrow or sharp melting range
- Yield a **clear melt crust below** body temperature or **dissolve rapidly** in the body fluid
- Be **inert and compatible** with a variety of drugs
- Be **non-irritating and non-sensitizing**
- Have a **wetting and emulsifying** properties

Suppository bases

Ideal properties of suppository bases [11]

1. Remain solid at storage temperature
2. Soften, melt or dissolve in the rectal fluid
3. Readily release therapeutic agent
4. Non-irritant & non-toxic to the rectal mucosa
5. Stable if heated above mp & then cooled

6. Easily pourable in to the mould
7. Never adhered to mould's wall
8. Have adequate contraction upon cooling
9. Never chemically interact with therapeutic agent
10. Chemically & physically stable during shelf-life
11. Have wetting and emulsifying properties
12. Have an acid value of less than 0.2 ,a saponification value of 200-245 and an iodine value of 7 , if the base is fatty.

- **Saponification number** of the ester represents the number of milligrams of alkali (NaOH or KOH) required to hydrolyse 1 g of the ester.
- When ester is an oil or fat the esterification leads to the formation of a soap, that is why esterification reaction is called 'saponification'. As most of the mass of oil or fat is in the fatty acids, it is a measure of the average molecular weight (or chain length) of all the fatty acids present.
- **Acid number** is the number of milligrams of KOH required to neutralize 1 g of the fatty acid
- The acid number is a measure of the number of carboxylic acid groups in the fatty acid

Types of suppository bases

1. Fatty (oleaginous) bases

   Eg. Cocoa butter

2. Water-miscible or water soluble bases

   Eg. Glycerinated gelatin

   Polyethylene glycols

3. Miscellaneous bases mixtures of oleaginous & water soluble or water miscible materials

I. Fatty (oleaginous) base [two types]

1. Natural oleaginous bases

Eg. Cocoa butter

2. Semi-synthetic/synthetic bases

Eg. Mixtures of triglycerides [higher saturated fatty acids] & di/mono-glycerides

II. Water-soluble & water-miscible bases

Cocoa butter (Theobroma oil =TBO)

- Natural material consisting of a mixture of fatty acid esters of glycerol e.g. glyceryl tripalmitate or tristerate
- Cocoa butter is safe, non-toxic and non-irritating
- Cocoa butter suppository has low m.p (30–36 ^{o}C)

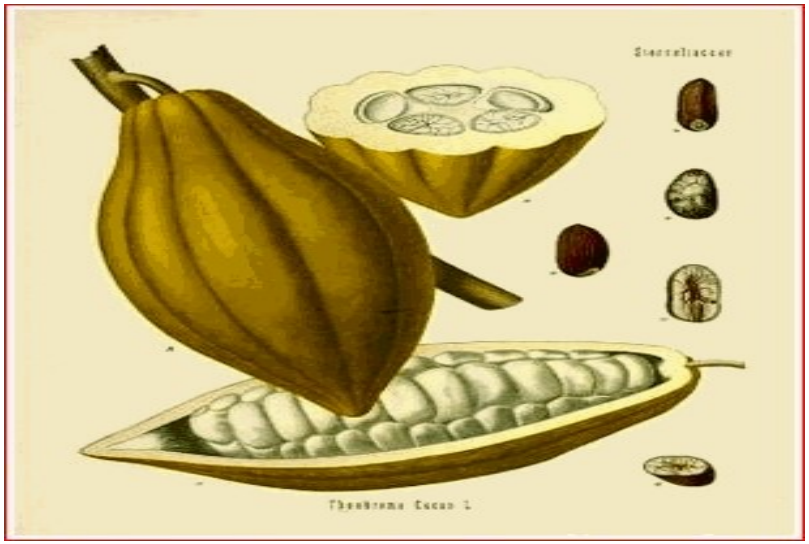
Reasons

- TBO has unsaturated (e.g. oleic acid) esters of glycerol
- Incorporation of lipophilic drugs into cocoa butter

How to overcome ?

- Increase melting temperature by adding 4% w/w Beeswax or 20% w/w Cetyl esters wax

Cocoa Butter (or Theobroma oil)



- A solid fat expressed from roasted seeds of Theobroma cacao.
- A pale yellow solid, becoming white on keeping, with a slight odour of cocoa and a bland taste
- M.P. < body temperature
- Slightly soluble in alcohol; benzene, chloroform, ether, light petroleum

Major problems related to TBO as a supp. base

- Polymorphism [α,β,β'& ɤ have melting point 20 ,34–35, 28,15°C. respectively]
- Has too low melting/softening point
- Can not be used in tropical or subtropical climate
- Leakage from the body, post insertion
- Soluble ingredients reduce its m.p [eg.Chloral hydrate,camphor,Thymol,salol,Phenol]
- Adherence to the mould
- Rancdificaion as unsaturated triglycerides oxidized
- Poor water absorbing capacity

Semisynthetic/Synthetic bases

- Developed to overcome shortcomings of TBO.
- Composed of mixtures of :
  - Triglycerides
  - Diglycerides
  - Monoglycerides

of higher saturated fatty acids

How to synthesis semisynthetic/synthetic bases ?

1. Hydrolyze vegetable oils to produce unsaturated fatty acids [FAs]

2. Hydrogenate the resulting FAs to get saturated ones

3. Re-esterify saturated FAs with glycerol by heating

Advantages of Semisynthetic/Synthetic Bases

- Safe, non-toxic and non-irritating
- Can be reheated above m.p during processing with out affecting their solidification temperature
- Resist oxidation since saturated via hydrogenation
- Have narrow d/ce b/n their melting &solidification pt.
- Can be used in tropical & subtropical climate
- Have good water absorption capacity as they contain partial triglycerides
- No need for mould lubrication prior to moulding

Disadvantages of Semisynthetic/Synthetic bases

- Brittle if rapidly cooled
- More fluid than T.O when melt, triggering drug sedimentation

Factors affecting performances of synthetic or semi-synthetic supp. Bases

- Melting point of the base
- Viscosity of the melt base

Effects of melting point of suppository bases

- Low melting bases (33- 37 °C) are used in suppository formulation intended for systemic therapeutic effect
- Supp. bases with m.p >37 °C are used in supp. formulations intended for local effect

Reason:

Softening but melting is sufficient to release drug for local effect from such suppository formulations

- Suppository base that offers a higher melting point should be used with a base soluble drug

Reason: Such drugs reduce melting point of the base

- Solubility of therapeutic agent within both molten base during production process and cooled base during storage affects its performance

Reasons

1. Drug precipitation following cooling
2. Formation of different drug polymorphic forms
3. Formation of drug crystals with different size fraction

More viscous melt bases as compared to less viscous melt bases have:

- Poorer spreadability on rectal mucosa
- Slower rates of drug release
- Poor diffusibility of the drug

Inferences

Selection of a suppository base must consider:

- Melting point of suppository base
- Viscosity of the molten base
- Drug solubility in the molten or cooled base

II. Water-soluble and water-miscible bases

1. Glycerol–gelatin base
2. Polyethylene glycols (PEGs) bases

Glycerogelatin base [Water soluble bases]

Formulation	Amount (% w/w)
• Gelatin	20
• Glycerol	70
• Aqueous phase	10

Procedure

- Dissolve gelatin with glycerol at 100 °C
- Dissolve drug in water
- Mix aqueous phase with glycerl phase by stirring
- Pour the dispersed system into suppository mould

Alternative method

- Heat the aqueous phase
- Dissolve gelatin in heated aqueous phase
- Add to the heated glycerol
- Mix with stirrer
- Pour into suppository Mould

Note:

- Glycerol-gelatin bases are mostly used for laxative purposes and in vaginal dosage forms
- A higher proportion of gelatin in the mixture makes it more rigid and longer acting

Suggestion

Adding paraben based preservatives into glycero-gelatin suppositories is mandatory . Do you agree **? Why?**

Strength of glycerogelatin base suppository depends on amount of gelatin in the formulation

- Supp. is softer as % of aqueous phase increases
- Supp. is stronger as % of gelatin increases

Example: **Gelatoglycero suppositories**

- Gelatin 32.5% w/w
- Glycerol 40% w/w
- Aqueous phase 27.5% w/w
- **Urethral suppositories** :

Gelatin **:** Glycerol **:** Aqueous Phase = 3:1:1

% w/w of each component ???

Problems associated with Glycerol–gelatin supp.

- An associated physiological effect.
  - induce defecation ,thus relieving constipation or facilitating bowel evacuation prior to surgery
- Difficult to manufacture
- Hygroscopic :
  - Packaging?
  - Storage ?
  - Rectal mucosal dehydration and irritation
- Potential interactions with therapeutic agents

Gelatin interacts with drug at pH<4.7 & pH >5.3

Polyethylene glycol suppository bases [Water Miscible bases]

- Formed by mixing proportionate amount of low & high molecular weight PEGs
- The melting point of higher grades PEGs increases as their molecular weight increases

Example: the melting points of PEG -1000 and PEG -8000 are 37–40 ^{o}C and 60–63 ^{o}C, respectively.

- The melting point of PEG suppository bases, on average is ≈ 42 ^{o}C ,achieved and controlled using appropriate mixtures of PEG grade

- Higher melting point suppository base obviates need for storage under cold conditions
- Blending different molecular weights PEGs is used to control both melting point & physical strength of PEG-based suppositories.

Note:

Lower-molecular-weight PEGs, reduce m.p & brittleness of suppository bases.

e.g. PEG 400

❖PEG suppository base is hygroscopic

Problems

A. Storage problems: PEG bases can develop peroxides & become softened during storage

Remedy

- Use airtight & moisture-resistant packaging

B. Patient noncompliance due to its stingy effect on rectal mucus membrane

Solution

- Deep in to warm water prior to insertion into rectum

Excipients used in suppository formulation

- Surface-active agents
- Agents to reduce hygroscopicity
- Agents to control m.p of the base.

Surface-active agents

- Enhance wetting properties of supp. base with the rectal fluid increasing drug release/dissolution.
- Mainly reserved for supp.formulations composed of lipophilic suppository base and/or lipophilic drug

Examples :

- Sorbitan esters
- polyoxyethylene sorbitan fatty acid esters.

Agents to reduce hygroscopicity

- Agents that reduce hygroscopicity, e.g. **colloidal silicon dioxide,** may be included in water-soluble and water-miscible suppository bases to reduce uptake of water from the atmosphere during storage

Result: Enhanced physical and chemical stability of supp. Dosage form /therapeutic agent

Agents to control m.p of supp. base

- Melting point of base is manipulated to enhance mechanical properties & physical stability of suppository in response to the deleterious effects of storage at higher temperature and/or the presence of a suppository base soluble therapeutic agent

Excipients that increase m.p of suppositories prepared using fatty bases:

- Beeswax (white or yellow wax)
- Stearic acid
- Stearic alcohol
- Colloidal silicon dioxide
- Magnesium stearate
- Bentonite.

- **Excipients that reduce m.p of fatty suppository base within the rectum:**
  - Glyceryl monostearate
  - Myristyl alcohol
  - Polysorbate 80
  - Propylene glycol

1. The melting point of PEG-based suppositories may be controlled by altering the grade of PEG used

How??

1. Inclusion of higher-molecular-weight PEG increases melting point .
2. Incorporation of low-molecular-weight PEG (! PEG- 400) lowers melting point

Factors to be Considered prior to the start of manufacturing suppository

1. Avoid incorporation of water into supp.
2. Hygroscopicity of the base
3. Density of incorporated drug
4. Viscosity of the base
5. Brittleness of suppository
6. Volume contraction
7. Incompatibilities
8. Packaging
9. Storage/Labelling
10. Rate of drug release

Avoid incorporation of water into supp.

Reasons

- Accelerate oxidation of fatty bases
- Increase degradation rate of sensitive drugs
- Support microbial growth, initiating use of bacteriostatic agents
- Dissolved drug may crystallize out from suppository base following water evaporation

Rate of drug release from suppository bases

Base	Drug Solubility	Drug release rate
Oily	Oil soluble	Slow
oily	Water soluble	Rapid
Water miscible	Oil soluble	Moderate
Water miscible	Water miscible	Rapid

Note

Release & onset of drug action from suppository base depends on:

- Liquefaction of the base
- Dissolution of the drug
- Diffusion of drug via mucosal layer
- Rate of drug absorption via rectal mucosa

Preparation methods [2]

1. Compression or Cold process

- Drug is mixed with shredded vehicle
- The mixture is then forced into a mould
- Subsequently extruded

2. Fusion or Hot process : Principal method

How to proceed ??

- **Melt the base [Hint: start with a base having higher m.p]**
- **Incorporate the drug into the melted base**
- **Pour the mass into mould just before it congeal**
- **Scrap off any excess mass**
- **Let the poured mass congeal**
- **Remove suppository from the mould**
- **Pack individually into plastic [PVC] or Aluminum foil packs**

General Procedure

1. Calculate amount of ingredients required
2. Prepare the mould using soapy H_2O or Arachis oil if the base has low contraction volume or remain adhere to wall of the mould after congealing
3. Prepare the base
4. Prepare the medicament[insoluble or soluble solid drug]
5. Melt the base
6. Incorporate medicament
7. Fill mould to overflowing level
8. Remove excess after 2-3 minutes
9. Open the mould after 10 minutes standing in cool place & remove the suppositories

Displacement value [DV]

The ratio of the weight of the drug to the weight of base displaced by the drug ,i.e.,

DV =Total weight of drug / weight of base displaced

- Weight of drug needed for total number of suppositories = **weight of drug per suppository x number of prepared suppositories**
- Amount of base displaced by drug's = **Nominal weight of suppository base - Actual weight of suppository base**

Example

- If drug concentration in each suppository should be 10% and six suppositories are to be prepared in 1 g mould and total weight of six medicated suppositories is 6.11 g, compute the following requirements:

1. Determine blank weight of the six suppositories
2. Find amount of the base displaced by total drug
3. Determine DV of a drug in a fatty base
4. Compute masses of base and drug in the six suppositories
5. Determine percentage of the base actually used

2. Compute the following requirements assuming production of 20 suppositories, each containing 400 mg of drug -X (DV= 1.5) using 2 gm mould.

Requirements:

1. Determine blank weight of the 20 suppositories
2. Find amount of the base displaced by total drug
3. Determine DV of a drug in a fatty base
4. Compute masses of base and drug in the twenty suppositories
5. Determine percentage of the base actually used

Quality Control parameters for suppositories and pessaries

- ❖ Appearance
- ❖ Weight uniformity
- Disintegration time for rectal &vaginal tablets and capsules
- ❖ Melting (dissolution) behaviour
- ❖ Mechanical strength using hardness tester
- ❖ Content uniformity of active ingredient
- ❖ Drug release

Assignment on IPP-II

A. Prepare 20 suppositories containing drug-x[DV= 1.5] and drug-y[DV=2] in 4 g mould. Assuming that amount of drug-x and drug-y per 20 suppositories are 600 mg & 400 mg, respectively, answer the following questions.

Requirements:

1. Determine blank weight of the 20 suppositories
2. Find amount of the base displaced by total drug
3. Compute masses of base and each drugs in the twenty suppositories
4. Determine percentage of the base actually used
5. Determine percentage of each drugs

B. In the preparetion of 10 Paracetamol[DV=1.5] 720 mg suppositories using 4 g mould perform the necessary computations and write a formula for paracetamol supp.

C. Ten 15% Bismuth subgallate suppositories are designed to be prepared in a 2 g mould. The displacement value of Bismuth subgallate is 3.

1. Determine nominal weight of ten suppositories
2. Compute displaced base upon addition of total drug
3. Compute masses of base and drug in the ten suppositories
4. Determine percentage of the base actually used

D. If a private prescription is presented to you as follow, perform below mentioned requirements

Rx

- Drug X ……500 µg/5 g tsp
- Drug Y ……500 mg/5 g tsp
- Effervescent granules qs …… 360 g
- Sig: dissolve 1 tsp & drink; Repeat dose every 6 hrs

Required:

1. Compute amount of each ingredient in Rx
2. Write master formula for Rx
3. Calculate total dose & duration of therapy

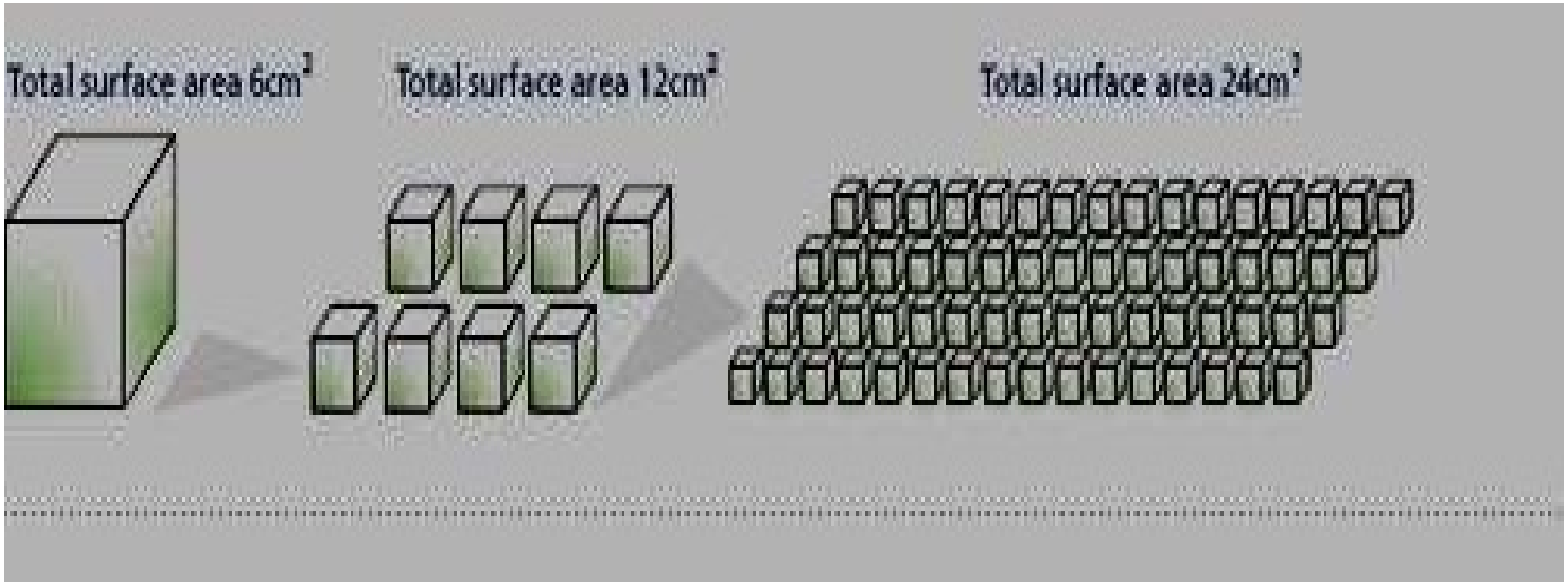
Unit 3. Micromertics

- Particle size and size distribution
- Methods for determination of particle size and size distribution
- Particle shape and surface area
- Methods for determination of surface area
- Derived properties of powders [densities, porosity, packing arrangement, flowability]

What is micromertics ?

Definition:

- It is the science and technology of small particles
- The unit of particle size used is the micrometer[μm] micron[μ] and equal to 10^{-6} m
- As particle size decreases, surface area increases



- Knowledge and control of particles size is important in pharmacy and materials science
- Size & surface area of a particle can be related to the physical, chemical & pharmacologic properties of drugs, as disclosed below:

A. Dissolution & Release

- Particle size & surface area influence drug release from a dosage form
- Higher surface area allows intimate contact of drug with dissolution fluids in vivo & increases dosage form dissolution & drug solubility

B. Absorption & drug action

- Particle size & surface area influence drug absorption & subsequently its therapeutic action
- The higher the dissolution is the faster the absorption & hence quicker & greater drug action

C. Physical stability

- Particle size in a formulation influences physical stability of suspensions & emulsions
- The smaller the size of the particles, the better the physical stability of these dosage forms

D. Dose uniformity

- Good flow properties of granules & powders are important in tablets & capsules manufacturing

Methods for determining particle size & size distribution

1. Optical microscopy (range: 0.2 –100 μm):

- The microscope eyepiece is fitted with a micrometer by which the size of the particles may be estimated

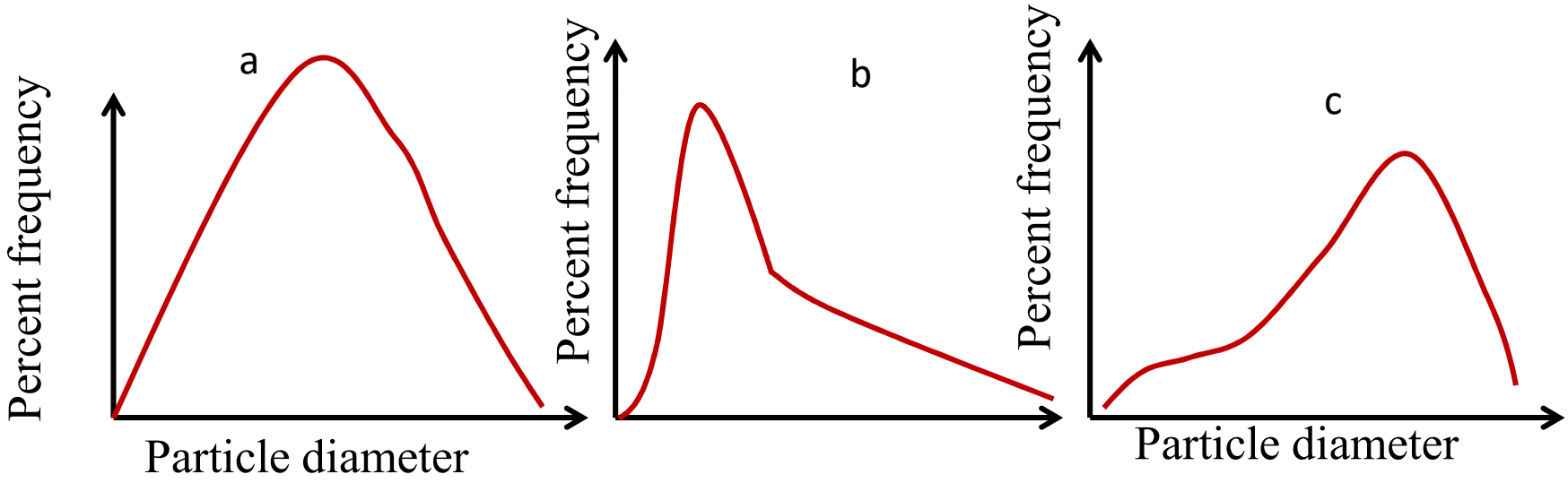
2. Sieving (range: 40 – 9500μm)

- Standard sized sieves are available to cover a wide range of sizes.
- These sieves are designed to sit in a stack so that material falls through smaller & smaller meshes until it reaches a mesh which is too fine for it to pass through

- Stack of sieves is mechanically shaken to promote passage of solid particles through each sieve
- Fraction & hence percent of particles retained on each sieve is determined by weighing & dividing residue on each sieve by total weight of the powder sample.
- Achieved result depends on duration & manner of agitation

Particle size distribution

- Not all particle populations have symmetrical normal size distributions, thus frequency distributions of such populations exhibit skewness
- Positive & negative skewness show existence of more larger & smaller particles, respectively



Frequency distribution curves corresponding to (a) normal distribution, (b) positively skewed distribution and (c) Negatively skewed distribution

Derived properties of powders

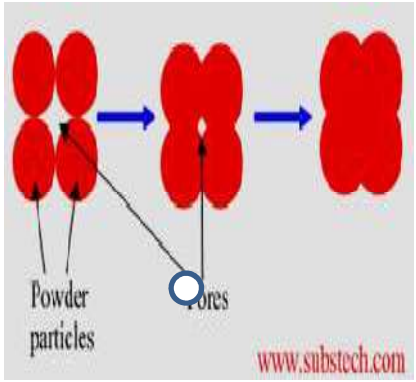
- Densities [Bulk density, Tapped density, True density]
- Volume [Bulk volume, Tapped volume, True volume]
- Porosity
- Packing arrangement
- Flowability

Density [True density, Bulk density, Tapped density]

- Density = Mass/volume

➢ **True density:**

Density of particles that excludes interparticle &/ intraparticle void spaces



➢ **Bulk density** = Mass/ untapped volume

Note: Bulk density of a powder is always less than its true density since powder contains intraparticular pores or interparticulate air-filled voids hence, bulk density of a powder is dependent on particle packing & changes as powder consolidates.

➢ **Tapped density** = Mass/ Tapped volume

- Porosity is the ratio of void space to bulk volume of the particles

$$\varepsilon = 1 - V_p / V_b = Void / \text{Bulk volume}$$

Note

- For powders having comparable true densities, an increase in bulk density causes a decrease in porosity. This increases the number of interparticulate contacts and contact areas and causes an increase in adhesion/ cohesion

Flowability of particles depends on:

- **Particle shape:** Powders with similar particle sizes but dissimilar shapes can have markedly different flow properties owing to differences in interparticle contact areas. For example, a group of spheres has minimum interparticle contact and generally optimal flow properties, whereas a group of particle flakes or dendritic particles has a very high surface-to-volume ratio and poorer flow properties.

- **Particle's texture**: particles with very rough surfaces will be more cohesive and have a greater tendency to interlock than smooth surfaced particles

- **Density of particles**: Because powders normally flow under the influence of gravity, dense particles are generally less cohesive than less dense particles of the same size and shape

Surface Forces

- Reduction of electrostatic charges can improve powder flowability.
- Electrostatic charges can be reduced by altering process conditions to reduce frictional contacts.
- Moisture content greatly affects powder's flowability
- Adsorbed surface moisture films tend to increase bulk density and reduce porosity. Drying reduces cohesiveness and improve the flow.
- Hygroscopic powders: stored and processed under low humidity conditions.

Unit 4:Powders and granules as a dosage form

Objectives of size reduction

- to produce smaller particles
- to facilitate mixing of powders
- to increase surface area
- to increase adsorptive properties
- to reduce the bulk volume of material
- to improve transportation

Factors affecting size reduction

- Toughness
- Stickiness
- Temperature
- Bulk density
- Surface hardness
- Material structure
- Moisture content
- Economical factors

Powder mixing

- Powders may be blended by spatulation, trituration, sifting &/or tumbling
- Spatulation: Mixing small amount of powders placed on paper or ointment tile by movement of spatula in them
- Can not be used for blending large powder mass
- Trituration used to mix & grind powder using glass or porcelain mortar & pestle

Challenges of powder dosage forms

- Demixing: Separation of previously mixed powder components due to difference in particle size, density,etc
- Liquefaction of components at room temperature

Example: A blend of phenol ,thymol ,salol or camphor forms eutectic mixtures at room temperature

Remedy:

Physical separation of each of such trouble agents using talc, light magnesium oxide or magnesium carbonate

‘Powder' as a dosage form

- Refers to formulation containing a drug powder mixed with powdered excipients to produce final product **or**
- An intimate mixture of dry, finely divided chemicals or drugs that may be intended for internal or external use.
- Function of added excipients depends upon the intended use of the product
- Powders for oral use may contain for instance colouring, flavouring and sweetening agents

Dispensing powdered and granulated products

- Bulk powders or granules for internal use
- Divided powders or granules (i.e. single dose) for internal use minimum weighable weight =120 mg
- Dusting powders for external use.

Other preparations presented as powders or granules

- Insufflations for administration to ear, nose or throat
- Antibiotic syrups to be reconstituted before use
- Powders for reconstitution into injections
- Dry powder inhalers

Advantages of powder and granule products

1. Solid preparations are more stable than liquid ones

Example

- Powders for antibiotic syrups are stable [2-3 years] than reconstituted ones [1-2 weeks]
- Powders for reconstitution into injections

2. Convenient form to dispense drugs with a large dose

Eg: The dose of Compound Magnesium Trisilicate Oral Powder is 1-5 g to be dispersed later in water and swallow by patient as a draught.

3. Have faster dissolution rate than tablets or capsules
4. Provides faster absorption rate of drug than from the corresponding tablet or capsule, if drug absorption rate is dissolution rate limited

Disadvantages of bulk powders & granules

1. Less convenient to carry by patient
2. Problem of masking unpleasant tastes
3. Not suitable for administering potent drugs with a low dose due to measuring problems
4. Volatile, hygroscopic, deliquescent or oxygen-sensitive substances cannot be dispensed as a powder dosage form

Types of dispensed powder dosage forms

Bulk powders:

- ❖ Appropriate for relatively non-toxic medicaments with a large dose [Compound MTS Oral Powder]
- ❖ Unsuitable for most products having hygroscopic, volatile or deliquescent ingredients

Divided powder

- Individual doses for potent drugs are separately wrapped
- Can be simple powder or compound powder
- Minimum weighable weight is 120 mg

Dusting powders : Two types

1. Medicated dusting powder

- Contain ingredients used for therapeutic, lubricant or prophylactic purposes, intended for external use.
- Sterility is rarely essential
- Dusting powders for lubricant purposes or superficial skin conditions need not be sterile but should be free from dangerous pathogens
- Minerals **!** talc and kaolin may be contaminated at source with spores of organisms causing tetanus ,gas gangrene and anthrax, should be sterilized prior to incorporation into product

2. Surgical {Absorbable} dusting powder

- Sterile dusting powders
- Applicable to open wounds, body cavities, burns & umbilical cords of infants
- Contain antibacterial agent & sterilisable diluents such as maize starch

Example:

- Chlorhexidine dusting powder
- Hexachlorophane dusting powder

- Talc dusting powder is a sterile cutaneous powder containing starch and purified talc.
- Talc is sterilized before incorporation with the starch, or final product is terminally sterilized
- Dusting powders are normally dispensed in glass or metal containers with a perforated lid.

Examples

Powder preparation	Uses
Hexachlorophane Dusting Powder	antibacterial
Talc Dusting Powder	prevent chafing
Canesten Powder (clotrimazole)	Antifungal
ORS	Rehydration
Compound MTS Oral Powder	Adsorbent & antacid
Chlorhexidine dusting powder	Antibacterial

Granules as a dosage form [Effervescent, Non-effervescent]

Granules are agglomerates of powdered materials prepared into larger, free flowing particles

Bulk granules : Dosage form containing less toxic but high dose drugs

Example: Bulk-forming laxative **!** MC granules

Divided granules

- Granulated products containing individually wrapped single dose

Example: Effervescent granules

Granulation

- Forming granules from primary powder particles
- Allows incorporation of Organoleptic ingredients
- On small scale, done using mortar& pestle & sieve
- Granulating agents : water, starch mucilage, gelatin, sucrose solution or co-solvents.
- Coherent material is pressed via suitable sieve
- Resulting granules are shaken gently on a finer sieve to avoid loose powder
- Dry compact granules in an oven at $\leq 60\ ^{O}C$

Reasons for granulation

- Prevent demixing of constituents
- Improve flow properties of the mix
- Improve compaction characteristics of mix
- Prevent caking of hygroscopic constituents
- Reduce dusting of toxic substances
- Increase compressibility
- produce particle-size uniformity, thus content uniformity

Effervescent granules

- Contain active drug , acids & alkaline components
- Acid & alkaline components react rapidly in the presence of water ,releasing carbon dioxide
- Usually dissolved or dispersed in water before administration, resulting in effervescence
- Resulting carbonated solution masks unpleasant [bitter or salty] tastes of any medicinal agents

Components of effervescent preparation

Acid source: Tartaric acid , Citric acid

Alkaline source: [Carbonate Sources]

- Sodium bicarbonate/ Sodium carbonate
- Potassium bicarbonate /potassium carbonate

- Combination of Tartaric acid & Citric acid should be used in the formulation of effervescent granule

Reasons

1. Tartaric acid alone forms granules that readily loose their firmness & crumble
2. Citric acid alone results in sticky mixture,thus difficult to granulate

Preparation method of effervescent granules

1. Fusion or dry method
2. Wet method

Fusion or dry method

Binding agent is one molecule of H_2O of crystallization obtained from each molecule of citric acid [$C_6H_8O_7.H_2O$]

Components having same sieve size are mixed using stainless steel spatula in env't with low humidity.

Why Stainless steel spatula ? & low RH env't ?

- Premature chemical reaction {-}
- Environmental moisture absorption {-}

Procedure

- Place mixed powder on a dish
- Put in an oven at 34-40 ^{O}C
- Heating releases H_2O of crystallization from citric acid
- Released water, dissolves portion of powder mixture
- Chemical reaction occurs releasing CO_2
- Both released H_2O & CO_2 form softened mass of powder with spongy texture
- Remove mass with a bread dough from oven
- Rub mass via sieve to yield granules of desired size
- Dry granules at 54 ^{O}C
- Pack dried granules immediately in tightly sealed container

Wet method

- Granulating agent is Alcohol or Hydroalcoholic Solution
- Not water of crystallization from citric acid
- Moistened mass of powder mixture is then treated in same way as for fusion method

Note

The ratio of effervescent ingredients is 1:2:3.4 for citric acid:tartaric acid:sodium bicarbonate

Example

1. A prescription calls for medicated effervescent granules containing 500 mg/5 g tsp in adequate quantity of effervescent granules to make 120 g.

Sig: Dissolve 1 teaspoonful in one-half of cool water & drink. Repeat the dose every 8 hours

Required: Compute actual quantities of each ingredients for the entire prescription & duration of therapy, i.e.,

A. Active drug
B. Citric Acid
C. Tartaric acid
D. Sodium bicarbonate
E. Duration of therapy

2.

R_x

Drug A …… ……400 mg per 5 g tsp

Effervescent granules qs …….. 350 g

Sig: Dissolve 1 teaspoonful in one-half of cool water & drink. Repeat the dose every 12 hours

Required:

1. Calculate amount of each components of R_x
2. write the master formula for R_x.
3. Compute duration of therapy

Exercise

Rx

- Drug X …….. 500 µg/5 g tsp
- Drug Y ……500 mg/5 g tsp
- Effervescent granules qs …… 360 g
- Sig: dissolve 1 tsp & drink;
- Repeat the dose every 6 hrs

Required:

1. Compute amount of each ingredient in Rx
2. Write master formula for Rx
3. Calculate total dose & duration of therapy

Unit 5. Diffusion & Dissolution

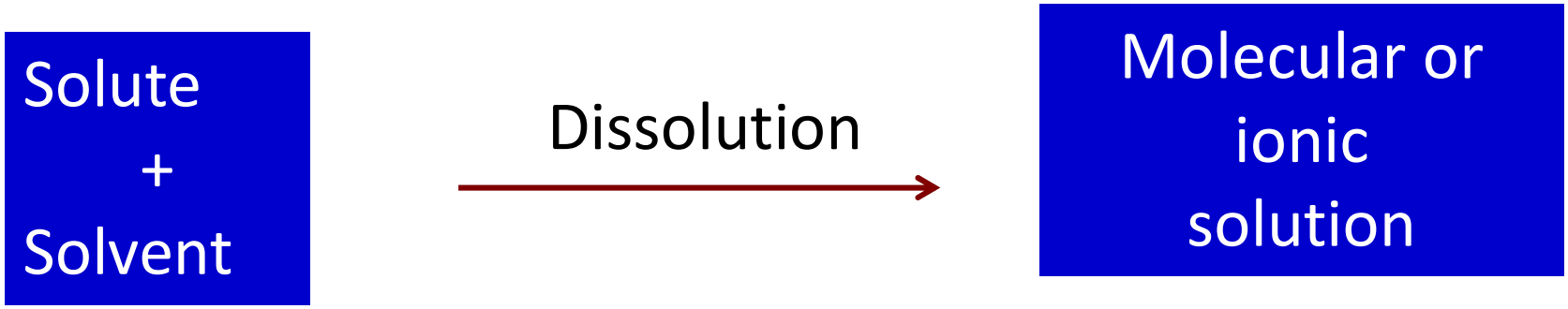
Mass transport

Molecular or ionic solution involves transfer of mass from a:

- ❖ solid to a fluid , eg: Solid + solvent = solution
- ❖ fluid to a fluid , eg: Liquid + heat = vapour

Dissolution

Process of conversion of solute to liquid solution



Solute transport

Can be achieved by various mechanisms

- Passive transport
- Carrier mediated transport
- Endocytosis

Passive transport:

- Transfer of solute from its higher concentration to lower concentration, thus it is down hill or concentration gradient transport
- Needs no energy or carrier molecule

Carrier mediated transport

Types[2]

A. Facilitated transport

- Transfer of substance follows concentration gradient
- Carrier molecule is demanded
- No energy expenditure

B. Active transport

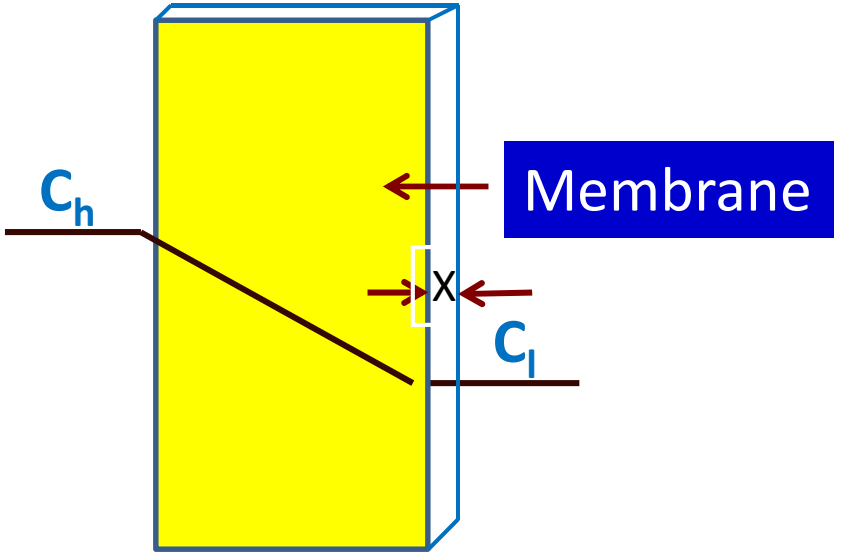
- Transfer of substance is up-hill
- Carrier molecule is needed
- There is energy consumption

Solvent transport [Osmosis]

- Movement of solvent molecules from its higher concentration to lower concentration
- Movement of solvent following concentration gradient of solute or electrochemical gradients

Diffusion via a membrane

- Drug molecules in solution spontaneously diffuse from a region of high chemical potential to one of low chemical potential



C= concentration
X= Membrane thickness

Rate of diffusion as per Fick's First law

$$\text{Rate of diffusion} = \frac{dM}{dt} = -\frac{DA[C_h - C_l]}{x}$$

Rate of diffusion

- Directly proportional to concentration gradient[C_h-C_l] ,diffusion coefficient [D] & area of membrane [A]
- Inversely proportional to membrane thickness[x]

Note:

- Diffusion coefficient, [diffusivity] though, appears to be a proportionality constant, it does not ordinarily remain constant.
- Diffusion coefficient is affected by concentration, temperature, pressure, solvent properties and chemical nature of the diffusant
- Therefore, D is referred to more correctly as a diffusion coefficient rather than as a constant

Sink conditions

- Conditions where drug concentration on one side of the membrane is significantly low as compared to its concentration on other side, i.e, $C_h >>> C_l$. **Why ?**
- Thus, Fick's first low is reduced as follow:

$$\text{Rate of diffusion} = \frac{dM}{dt} = -\frac{DAC_h}{x}$$

Dialysis

- In a healthy person kidney acts as crude filter removing toxic waste products[creatinine, urea] from the body while retaining such essential components as blood cells, plasma proteins & fats in the body's natural homeostatic balance. This process is called 'ultrafiltration process'
- If renal function is impaired, water & electrolyte balance is disturbed, toxic waste products build up in the blood & patient suffer from fluid overload.
- Under this conditions, an artificial method called dialysis that allow ultrafiltration to take place is adopted

What is dialysis?

- It refers to passage of solute together with solvent across biological membrane or artificial semipermeable membrane[made of cellophane or nitrocellulose] **or**
- *S*eparation process based on unequal rates of passage of solutes & solvent through microporous membranes
- Semipermeable membrane allows separation of a mixture of blood & dialysis fluid
- As dialysis fluid passes over the membrane, it removes water & waste products from the blood restoring homeostatic balance

Dialysis solution

- Has electrolyte concentration similar to normal extracellular fluid
- Prepared as concentrate solution to be diluted with water prior to use
- Its composition include Na, K, Ca, Mg, & chloride ions and $HCO3^-$ [from lactate or acetate]
- Glucose is added to dialysis solution to achieve necessary osmotic effect during dialysis

Note : Haemodialysis solutions need not be sterile as dialysis membrane within dialysis machine is microbial proof

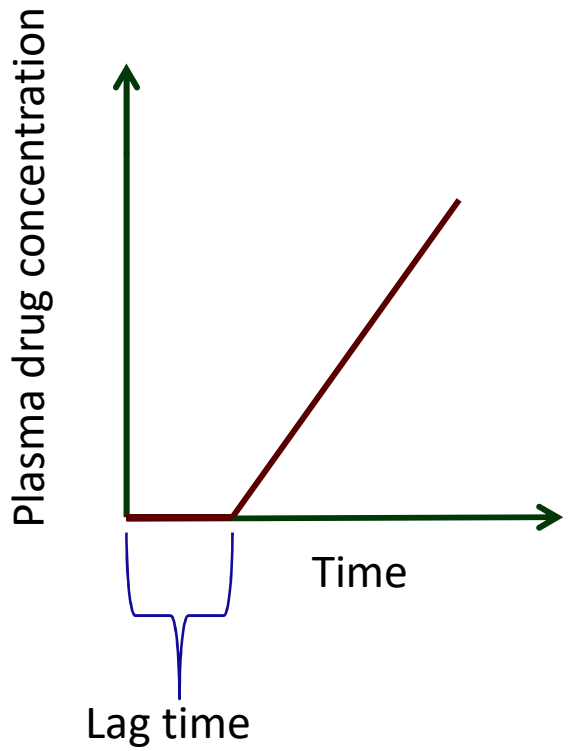
- **Haemodialysis** is used in treating kidney malfunction to rid blood of metabolic waste products while preserving high-molecular-weight components of the blood
- Patient's blood is passed over the dialyser [sterile disposable dialysis membrane] that allows solutes to be exchanged b/n the blood & dialysis fluid
- Pressure is applied to blood to induce ultrafiltration process
- Dialysis machines have programmed cycles to allow dialysis to be achieved as quickly & efficiently as possible

Note: Osmosis & dialysis are spontaneous processes

Lag time and burst effects

Lag time: Time elapsed for administered drug to have its onset of action

Example: Enteric-coated tablets



Significance of diffusion

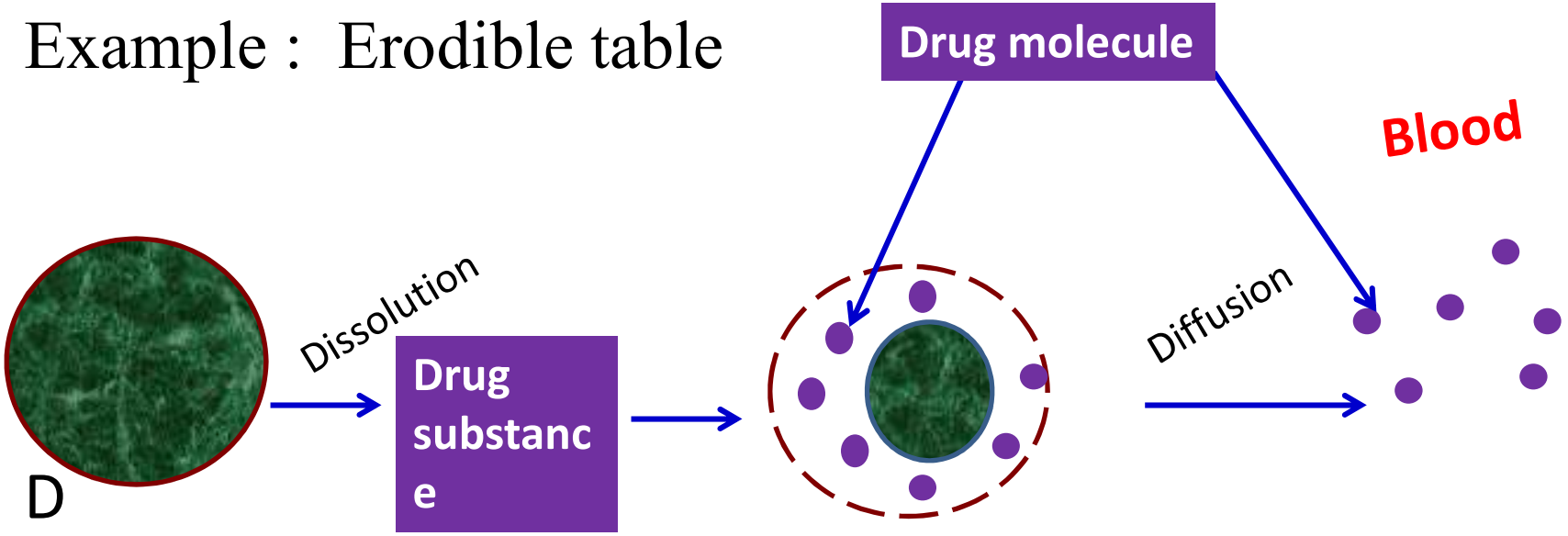
A. Drug release by diffusion[reservoir system, matrix system]

B. Drug absorption & distribution

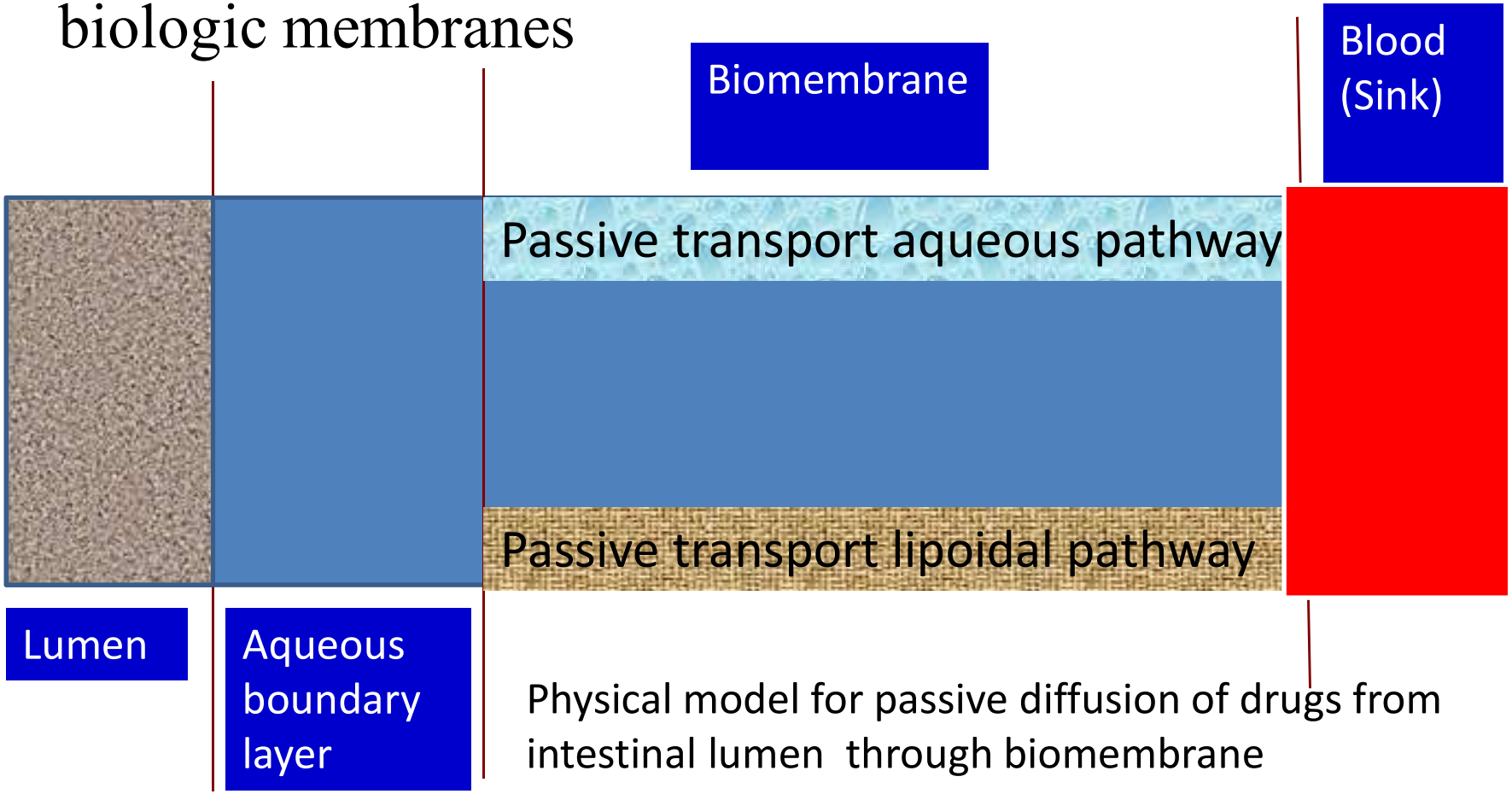
A. Drug release by diffusion[reservoir system, matrix system]

- Release of drug from a delivery system such as reservoir or matrix involves both dissolution & diffusion
- Drugs absorbed from site of absorption such as GI mucosa, skin, vagina, buccal cavity, etc by diffusion.

Example : Erodible table



- **B. Drug absorption & distribution**
- Drug absorption from extravasscular absorption sites into systemic circulation occurs by diffusion across biologic membranes



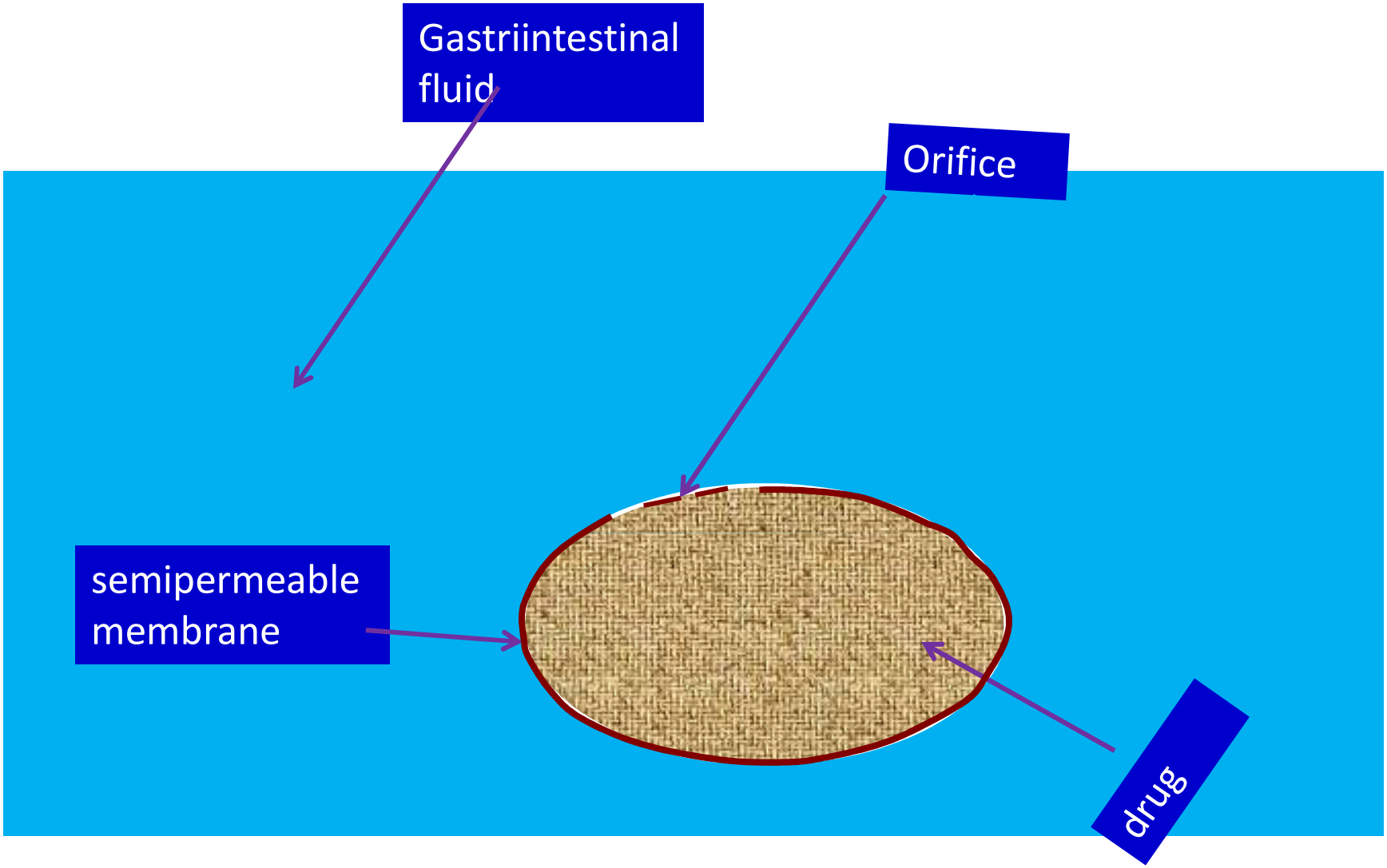
Physical model for passive diffusion of drugs from intestinal lumen through biomembrane

Significance of osmosis

Water soluble drug can be released from its reservoir such as osmotic pump by osmosis

Formation of osmotic pump

- Water soluble osmotically active drug or drug blended with osmotically active diluent is formulated into a tablet that is coated with cellulose triacetate barrier that serve as semipermeable membrane
- The membrane is permeable only to water
- Ingresses of water in addition to dissolving drug, create osmotic pressure[OP]
- OP then forces drug release via pump orifice
- The release rate is proportional to rate of drug fluid ingress from git


Gastriintestinal fluid
Orifice
semipermeable membrane
drug

Solubility & dissolution

- Solubility of a compound depends on physicochemical properties of solute & solvent, temperature, pressure & pH of the solution. It is determined under specific experimental conditions.
- Thus, solubility is *intrinsic* property of *drug substance*

➢ Can be altered only by chemical modification of drug molecule

- Dissolution is *extrinsic material property*

➢ Can be influenced by various chemical, physical or crystallographic means such as complexation, particle size, surface properties, solid-state modification, or solubilization enhancing formulation

Dissolution of particles

- For solid dosage forms, drug concentration at site of absorption is a function of dissolution rate of drug in the medium at that site
- Dissolution rate, $\left[\frac{dc}{dt}\right]$ is given by the **Noyes-Whitney equation:**

$$\frac{dc}{dt} = \frac{DS[C_s - C]}{h}$$

Where:

C= concentration at time, t

D = diffusion coefficient of the drug in the medium

S = Surface area of dissolving drug particles

h = thickness of the diffusion layer surrounding the particles

C_s = solubility of the drug in the saturated diffusion layer

Unit 6: Kinetics and drug stability

6.1. Introduction

6.2. Rates and order of reactions

6.3. Chemical & physical degradation

6.4. Factors affecting stability of drugs

65. Influence of temperature on reaction rate

6.6. Stabilization of drug products

6.7. Stability study

6.8. Prediction of shelf-life & beyond use time

Introduction

- Knowing the reaction rate is essential

Reason: How quickly a medicine acts can make the difference between life & death

6.2. Rates and order of reactions

A rate is a change in some amount of drug per unit of time

Importance of the rate process

- Enables drug producer to demonstrate that drug product remain stable for reasonable length of time during storage
- Assists pharmacist to know drug potential instability
- Ensures physician , pharmacist & patient that the prescribed drug reaches site of action in sufficient concentration

Fields of rate process:

- **Stability and incompatibility**: Rate process can lead to inactivation of the drug through decomposition or conversion into inactive or toxic form
- **Dissolution**: Main concern is the rapidity with which a solid dosage form is changed to molecular solution
- **Pharmacokinetics**: Concerns with the rate of drug absorption, metabolism and excretion
- **Drug action at molecular level**: Generation of a response by a drug is a rate process

- **Rate process** provides a rational approach to stabilization of drug products and prediction of shelf- life and optimum storage conditions.

Example: Thiamine HCl is most stable at pH 2-3 and is unstable at pH above 6. If this is combined with a buffered vehicle of say pH 8 or 9 the vitamin is rapidly inactivated

- Knowing rate at which a drug deteriorates when exposed to various hydrogen ion concentrations allows one to choose a vehicle that will retard or prevent the degradation

- In general, reaction kinetics is the study of rate of chemical change and the way in which this rate is influenced by:
  - concentration of reactants & products
  - other chemical species which may be present,
  - such factors as solvent, pressure & temperature
  - Ionic strength

Reaction kinetics: is the study of rate of chemical change and the way in which this rate is influenced by conditions of concentration of reactants and products, solvent, ionic strength and temperature

Reaction Rate :

- is the velocity with which a reactant or reactants undergo chemical change
- Mathematical description of the rate of change of drug concentration with respect to time

- The rate, velocity or speed of a reaction is given by the expression dc / dt where dc is increase or decrease of concentration over a time interval dt
- Rate, velocity or speed of reaction is given by: ± **dc/dt**

This expression gives the increase (+) or decrease (-) in concentration (C) within a given time intervals (dt)

Order of reaction [2 types]

- The order of a chemical reaction refers to the way in which the concentration of the reactant influences the rate.
- The two most common order of reaction associated with pharmaceuticals include:
  - Zero-order reactions
  - First order reactions

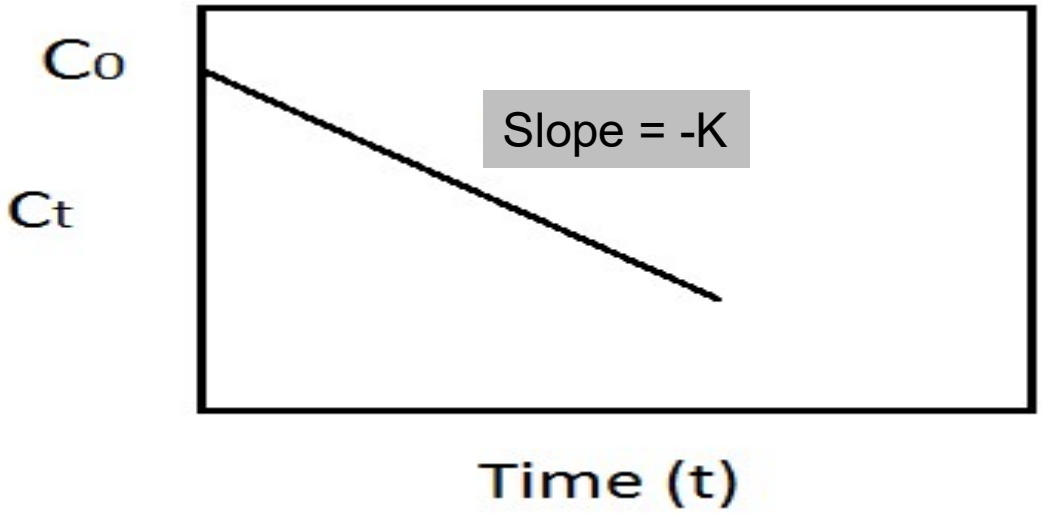
Zero-order rate reaction

- If the rate does not change when [A] doubles, the rate does not depend on [A], that is ,the rate depends on [A] raised to the zero power, $[A]^0$.The reaction is zero order in A and overall
- Loss of drug is independent of concentration of reactant since drug loss occurs at constant rate with respect to time [eg: 1mg/ml/hr]
- Can be mathematically expressed as follows:

$$-dc/dt = [C]^o K^o = K^o$$

where dc = change in concentration with respect to change in time, dt

The rate equation can be integrated b/n the initial concentration, C_0, at t = 0, and C_t, after time (t) and given by $C_t = Co - k_o t$



- The half-life ($t_{1/2}$) of a drug product is the time it takes for the drug product concentration to reach half its initial value.
- The formula to compute $t_{1/2}$ depends on the type of order of reaction by which the decomposition of the drug product occurs.

$$t_{1/2} = \frac{Co - 1/2Co}{ko}$$

$$t_{1/2} = Co/2K_o$$

Note

The half-life of zero-order reactions is directly proportional to initial concentration of drug products

$$t_{10\%} = [Co - o.9C_o]/K_o$$

$$t_{10\%} = Co/10K_o$$

Example

Assume that drug -X degrades by a zero-order process with a rate constant of 0.05 mg/ ml/year at room temperature. If a 1% solution is prepared and stored at room temperature answer the followings:

1. What concentration will remain after 18 months?
2. What is the half-life of the drug-x?

Solutions

Givens: K_o= 0.05 mg/ ml/year, C_o = 1% solution, t= 18 months

Q_1.

Required: C_{18} ? $t_{1/2}$?

$C_{18} = C_0 - K_0\, t_{18}$

= 10mg/ml - 0.05 mg/ml/year x 1.5 year

= 10mg/ml - 0.075 mg/ml

= <u>9.925 mg/ml</u>

Note: The remaining amount of Drug-x after 1.5 years is 9.925 mg/ml

Solutions

Q_2.

$t_{1/2} = 0.5C_0 / K_0$

$= [0.5 \times 10\text{mg/ml}] / 0.05\ \text{mg/ml/year}$

$= \underline{100\ \text{years}}$

Note:

Drug-x looses 50% of its initial concentration 100 years later if stored at room temperature

First order: If the rate doubles when drug concentration doubles, the rate depends on conc. raised to the first power, $[C]^1$. Thus, the reaction is first order with respect to A and first order overall

A. $dc/dt = -K_1C$

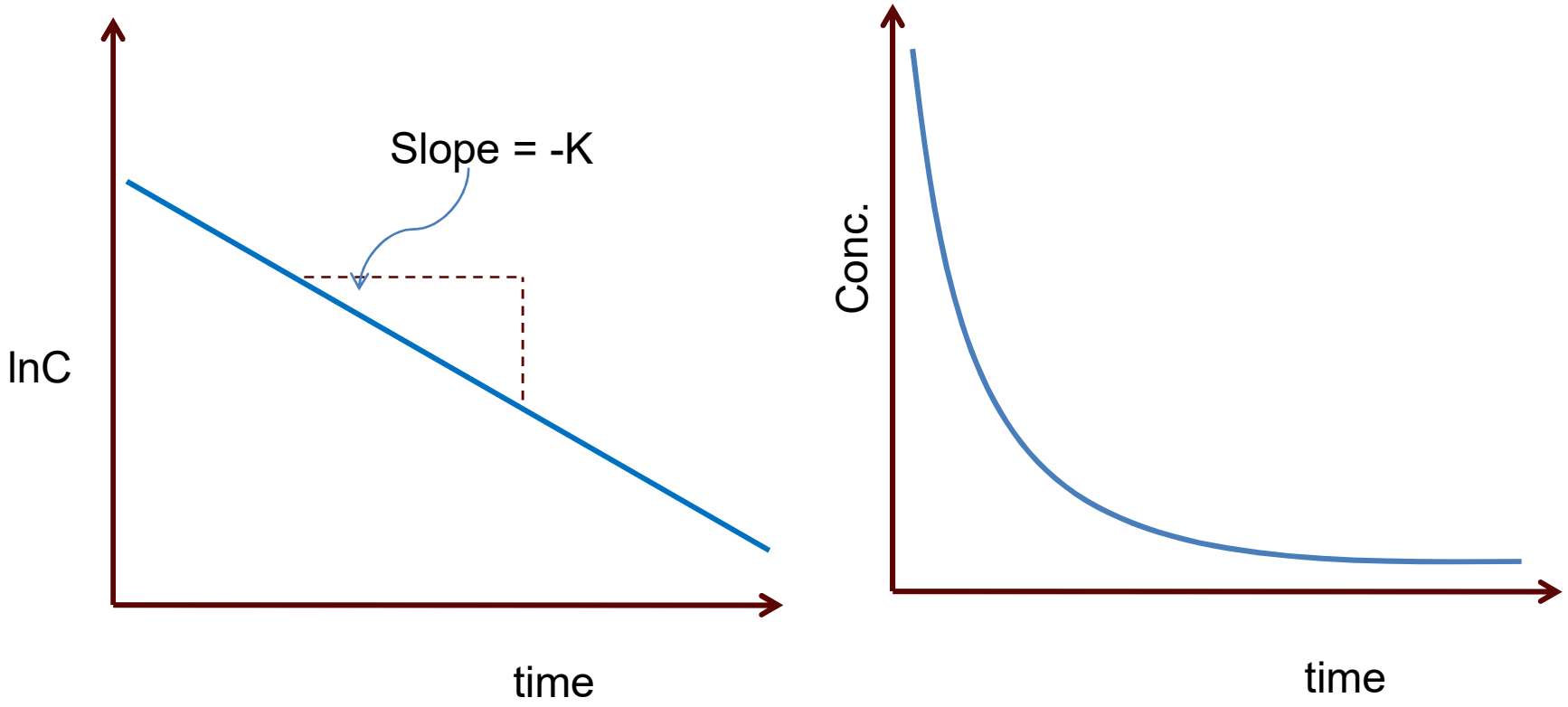
$\ln C_t = \ln C_o - K_1 t$

B. $t_{1/2} = 0.693/K_1$

Note : Half-life of first-order reactions is independent of initial concentration of the drug product.

Thus, the unit of K_1 is time^{-1}

C. $t_{10\%} = \ln[C_o - 0.9C_o]/K_1 = 0.105/K_1$



First order kinetics

Example

- A 5 gm/100 ml solution of drug X is stored in a closed test tube at 25°C. If the rate of degradation of the drug is 0.05 day^{-1}, calculate the time required for the initial concentration to drop to:

i. 50% (half-life) of its initial value

ii. 90% (shelf-life) of its initial value

Solution

Givens: $\mathbf{C_0 =}$ 5 gm/100 ml , $K_1 = 0.05\ day^{-1}$

Required = i. Half-life = ? Shelf-life = ?

i. $t_{1/2} = 0.693/ K_1$

$= 0.693/ 0.05\ day^{-1}$

$= \underline{13.860\ days}$

ii. $t_{10\%} = 0.105/ K_1$

$= 0.105/0.05$

$= \underline{2.1\ days}$

Apparent (Pseudo) Zero-Order Reactions for Suspensions

- Suspensions (e.g., Amoxil®, or Maalox®) are dosage forms in which the concentration of a drug exceeds the solubility.
- Suspension formulations, thus, have solid particles suspended in a solution of drug.
- Decomposition of drugs in suspensions depends on drug concentration in the solution as shown below:

- The rate of decomposition of A in solution, therefore, is given by the first-order expression:

$$dA/dt = -k_1[A]soln$$

- The excess solid drug present in suspension dissolves continuously to replace portion of drug converted to product from solution, thus [drug] in solution, i.e. , ([*A]soln)* remains constant.
- One can write k_1 *[A]soln* = k'_o , making decomposition process an apparent zero-order process, although the actual decomposition of the drug from the solution is first order.

- The above rate equation, therefore, can be rewritten as $dA/dt = -k'_0$ and the integrated form of the apparent zero-order rate equation is expressed as

$$A_t = A_0 - k'_0 t$$

Note : k'_0 *is the apparent [pseudo]* zero-order rate constant

Example

An aqueous suspension of drug- X contains 200 mg of drug- X per teaspoon (5.0 ml). The solubility of drug- X at 25°C is 1 g/350 ml in water, and the first-order rate constant for degradation of drug- X in solution at 25°C is $3.9 \times 10^{-6}\, sec^{-1}$

Calculate:

(a) the zero-order rate constant

(b) the shelf life of the liquid preparation.

Answer:

(a) $k'_0 = k_1[A]soln$

$= (3.9 \times 10^{-6}\ sec^{-1})(1\ g/350\ ml)$

$= \underline{1.1x10^{-8}\ g/ml\text{-}sec}$

(b) $t_{90} = 0.1[A_0]/\ k'_0$

$= (0.1)(0.04\ g/ml)/\ 1.11 \times 10{-}8\ g/ml\ sec{-}1$

$= 3.6 \times 105\ sec$

$= \underline{4.2\ days}$

Exercise

A. A pharmacist weighs exactly 10 g of a drug and dissolves it in 100 ml of water. The solution is kept at room temperature, and samples are removed periodically and assayed for the drug. The pharmacist obtains the following data

Time in hr	Conc in mg/ml
0	100
2	95
4	90
6	85
8	80
10	75
12	70

Required

1.Determine order of the reaction

2.What is the rate constant *k*?

3. What is the half-life?

Time (min)	Drug A (mg)
10	96.0
20	89.0
40	73.0
60	57.0
90	34.0
120	10.0
130	2.5

Required

1.Does the decrease in the amount of drug-A appear to be a zero-order or a first-order process?

2.What is the rate constant *k*?

3.What is the half-life *t* 1/2?

4.Does the amount of drug A extrapolate to zero on the *x* axis?

5.What is the equation for the line produced on the graph?

Time (min)	Drug A (mg)
0.5	84.5
1.0	81.2
2.0	74.5
4.0	61.0
6.0	48.0
8.0	35.0
12.0	8.7

Required

1.Is the decomposition of this antibiotic a first-order or a zero-order process?
2. What is the rate of decomposition of this antibiotic?
3. How many milligrams of antibiotics were in the original solution prepared by the pharmacist?

D. A solution of a drug was freshly prepared at a concentration of 300 mg/ml. After 30 days at 25 °C, the drug concentration in the solution was 75 mg/ml. when will the drug decline to one-half of the original concentration

I. Assuming first-order kinetics,?

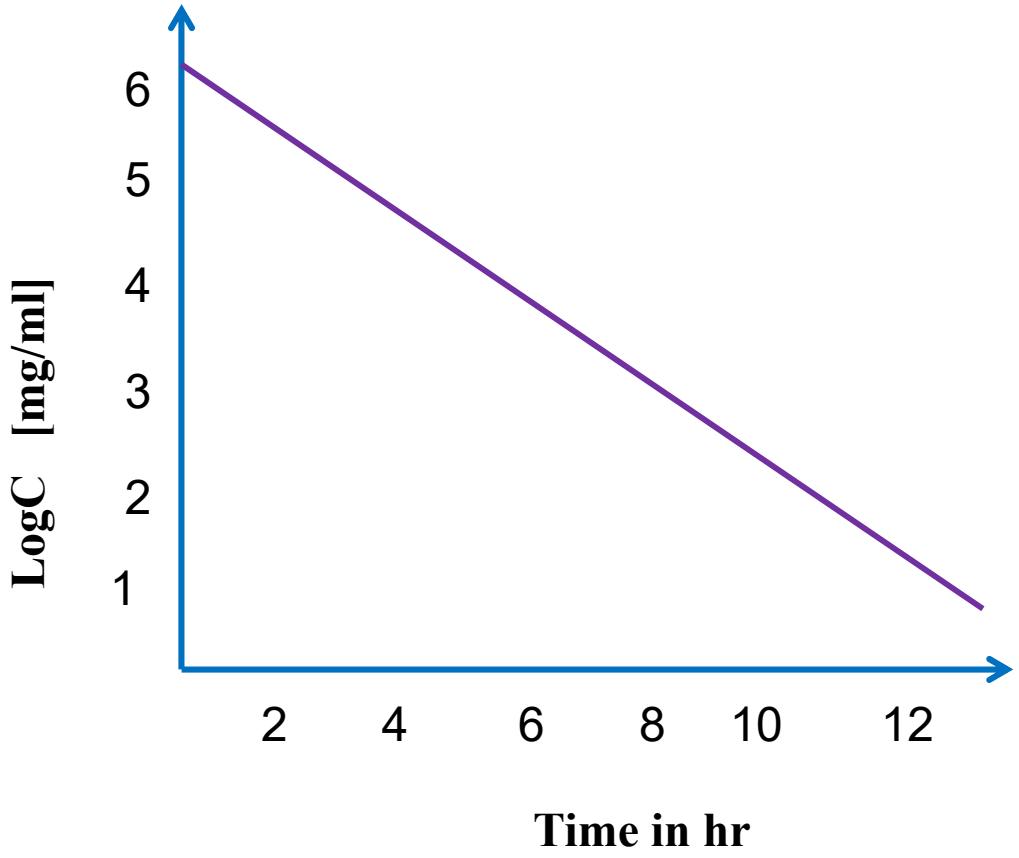
II. Assuming zero-order kinetics?

F. If the half-life for decomposition of a drug is 12 hours, how long will it take for 125 mg of the drug to decompose by 30%? Assume first-order kinetics and constant temperature.

G. The following data depicts plasma concentration profile after a single 600mg intravenous dose of ampicillin to an adult

Time (h)	Concentration [mg/mL])
1.0	37.0
2.0	21.5
3.0	12.5
5.0	4.5

1. Determine rate constant
2. Find Co
3. Find half-life
4. Determine equation of the line representing plasma conc. time profile



1. Determine half-life

Drug products must remain stable. Why ?

Reasons

- Chemical degradation of active agent lowers amount of therapeutic agent
- Product chemical decomposition process may give rise to potentially toxic agent
- Instability of a product can lower bioavailability of dosage form, hence reducing therapeutic efficacy of the drug
- Physical instability due to degradation of such excipients as product stabilizers, solubilizers, emullgent , suspending agents ,etc leads to creaming, mottling , caking, etc which in turn leads to product rejection and Compromisation of product integrity

6.4. Factors affecting drug stability:

1. pH:

- Acidic & alkaline pH influence decomposition rate of most drugs
- Many drugs are stable between pH 4 and 8.
- Weekly acidic and basic drugs show good solubility & faster decompose when they are ionized.
- Sometimes pH has a very serious effect on decomposition. As little as 1 pH unit change in pH causes a change of ten fold in rate constant. So during formulating a drug into a solution we should carefully prepare a pH – decomposition profile

2. **Temperature**: High temperature accelerate oxidation, reduction and hydrolysis reactions which lead to drug degradation

3. **Moisture:**

- Water catalyses such chemical reactions as oxidation, hydrolysis and reduction
- Water promotes microbial growth triggering microbial lead instability

4. **Light:** affects drug stability through its energy or thermal effect which lead to oxidation

5. **Pharmaceutical dosage forms:** solid dosage forms are more stable than liquid dosage forms for presence of water.

6. **Concentration**: Rate of drug degradation is constant for the solutions of the same drug with different concentration

   So, ratio of degraded part to total amount of drug in diluted solution is bigger than that of concentrated solution

7. **Drug incompatibility:** Reactions b/n components of pharmaceutical dosage forms itself or between these components and container

8. **Oxygen:** Exposure of drug formulations to oxygen affects their stability due to oxidation of oxygen sensitive drugs

6.5. Influence of temperature on reaction rate

- The effect of temperature on the reaction rate is described by the Arrhenius equation:

$$k = A\, e^{-Ea/RT} \quad \text{, Where}$$

K = reaction rate constant

- ✓ **Ea** = activation energy[the energy barrier that has to be overcome if a reaction is going to occur when two reactant molecules collide;
- ✓ **A** = frequency factor, which is assumed to be independent of temperature for a given reaction;
- ✓ **R** = universal gas constant,1.987 cal/mol/degree.;
- ✓ **T** = absolute temperature in Kelvin scale (273 +x °C)

- The Arrhenius equation can be rewritten in a linear form as:

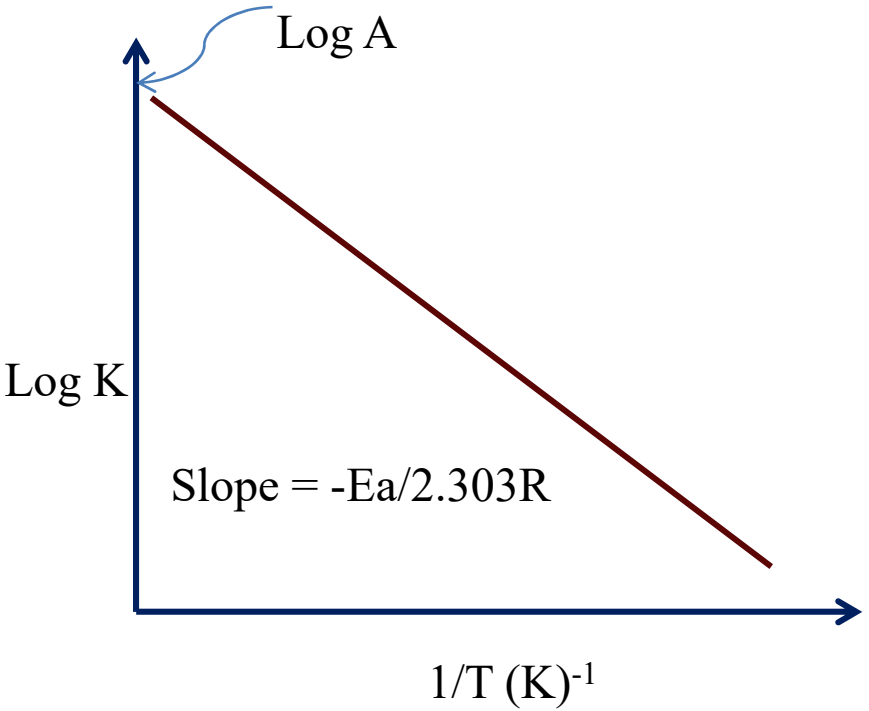
$$\ln k = \ln A - Ea/RT$$

or

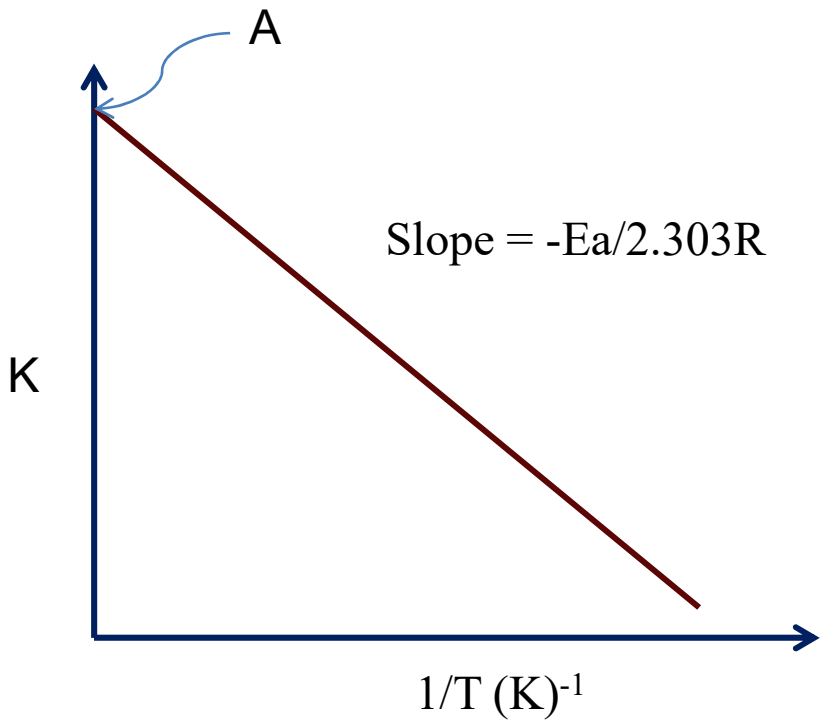
$$\log k = \log A - Ea/2.303\,RT$$

- Plotting log k as a function of 1/T on linear graph paper or k as a function of 1/T on semilog graph paper will give a straight line, with the slope equal to (–Ea/2.303R or–Ea/R) and the y-intercept equal to log A or lnA, respectively, as shown below.

Linear graph paper



Semilog graph paper



If the rate constants (k_1 and k_2) at two different temperatures (T_1 and T_2) are known, one can easily determine the activation energy and the frequency factor using the following equations.

$$\log k_1 = \log A - Ea/2.303\ RT_1$$

and

$$\log k_2 = \log A - Ea/2.303\ RT_2$$ Subtracting the second from the first, we have

$$\text{Log}(k_2/k_{1)} = \log A - Ea/2.303\ RT_2 - [\log A - Ea/2.303RT_1]$$

$$= Ea/2.303RT_1 - Ea/2.303RT_2$$

$$= [Ea\ (T_2 - T_1)]\ /2.303RT_2T_1$$

- If the activation energy and frequency factor at one temperature are known, one can easily determine the rate constant at any other temperature. This is important in the determination of expiration date of a new pharmaceutical product. However, some of the important underlying assumptions of this method are that :

I. breakdown is purely thermal

II. substance does not coagulate on heating, and

III. there is no change in the mechanism of degradation with a change of temperature

Example:

The rate constant for first-order degradation of a drug (activation energy is 20.0 Kcal/mol) in a solution (5.0 mg/ml) at 70°C is $1.50 \times 10^{-3}\ h^{-1}$.

1. Calculate the amount remaining after storage for one week at room temperature (25°C).
2. Calculate the amount remaining after one week if the drug is kept at 70°C.
3. Calculate the shelf life of the drug at room temperature.
4. Calculate the half-life of the drug at room temperature.
5. Calculate shelf-life of the drug at 70°C.
6. Calculate the half-life of the drug at 70°C.
7. Discuss what you learned from this exercise.

Solutions

Givens

$T_1 = 25^oC = [25 + 273]^o K = 298^o K$,

$T_2 = 70^oC = [70 + 273]^o K = 343^o K$

Ea = 20.0 Kcal/mol = 20,000Cal/mol

R = 1.98cal/mol/degree

$K_2 = 1.50 \times 10^{-3} h^{-1} = 0.0015\ h^{-1}$

1. $\text{Log}[\ 0.0015/K1] = [Ea\ (T_2 - T_1)]\ /2.303RT_2T_1$

$= 20000\text{cal/mol}(343\text{-}298)/(2.303\text{x}1.98\text{cal/mol/deg}\text{x}343\text{x}298)$

$= 900000/\ 467737.5$

$\text{Log}[\ 0.0015/K_1] = 1.92$

$0.0015/K_1 = \text{antilog } 1.92 = 83.18$

$K_1 = 0.015/83.18$

$= \underline{1.80 \times 10^{-5} h^{-1}}$ = first-order rate constant at 25°C.

- The amount remaining after storage (C) for one week at room temperature (25°C) can be found from $C = C_o\ e^{-K1\ t}$ $= \ln C = \ln co - k1t$

$C = 5\text{mg/ml}\ e^{-(0.000018)(24)\ \text{day-1(7) days}}$

$= \underline{4.98\ \text{mg/ml}}$

2. The amount remaining after storage (C) for one week at 70°C can be found from $C = C_o\ e^{-K2\ t}$

$C = 5\ \text{mg/ml}e^{0.0015\text{x}24\ \text{day-1x}7\ \text{days}}$

$= \underline{3.89\ \text{mg/ml}}$

3. Shelf life of the drug at room temperature can be found from

Shelf life $(t_{90}) = 0.105/K_1$

$= 0.105/\ 0\ 000018\ \text{hr}^{-1}$

$= 5833.33\ \text{hrs} \quad = \underline{243.1\ \text{days}}$

4. Half-life of the drug at 25 ^{0}C can be found from:

Half-life ($t_{1/2}$) = *0.693/K1*

= *0.693/0.00018*

= 38500 hrs

= 1604.2 days = 4.4.years

5. Shelf life of the drug at 70°C can be found from

Shelf life (t_{90}) = 0. 105/K_2

= 0.105/ 0.0015

= 70 hrs = <u>2.92 days</u>

6. Half-life of the drug at 70°C can be found from

Half-life ($t_{1/2}$) = *0.693/K2*

= *0.693/0.0015*

= 462 hrs

= <u>19.25 days</u>

7. Degradation at 70°C occurs 83 times faster than at room temperature, as shown below

$[k_2/k_1]$ = 0 .0015/0. 000018 = <u>83.33</u>

The implication is that the longer half-life and shelf life at room temperature compared to 70°C.

6.6. Stabilization of drug products

Destabilizing factor	Methods to stabilize	Examples of labile drugs
Temperature	Establish suitable storage conditions	
Hydrolysis	Buffering, use nonaqueous solvents such as alcohol, glycerin, or propylene glycol, make powder for reconstitution	Drugs containing ester, amide, etc bonds such as penicillin , cephalosporin
Photolysis	Use amber container	Hydrocortisone, folic acid, riboflavin, prednisolone, ascorbic acid

Destabilizing factor	Methods to stabilize	Examples of labile drugs
Isomerization	Establish optimal pH range	Adrenaline, pilocarpine, tetracycline, vitamin A, cephalosporin
Oxidation	Replace O_2 by nitrogen, add antioxidant or chelating agents	antibiotics, vitamins, oils, and fats , Phenolic compounds [phenylephrine, morphine] , steroids, catecholamine [dopamine & adrenaline]
Drug incompatibility	Avoid direct contact of incompatible drugs or excipients	Phenol and thymol

6.7. Stability study

Basic requirements of pharmaceutical products

- Efficacy: Optimum therapeutic level for specified period of time
- Safety: Minimum or no side effects
- Stability: The products should retain their properties during storage

This should guarantee the efficacy and safety

The **USP** defines the stability of pharmaceutical product as "extent to which a product retains within specified limits" and throughout its period of storage and use (i.e its shelf life) the same properties and characteristics that it possessed at the time of its manufacturer

- These stability data involves selected parameters that taken together from the stability profile
- Pharmaceutical products are expected to meet their specification for identifying purity, quality and strength throughout their defined storage period at specific storage condition.
- The stability of pharmaceutical product is investigated throughout the various stages of the development process.

Importance of stability studies

- Development of optimum formulation
  (preformulation studies)
- Finding the optimum storage conditions
  (temperature, light, humidity)
- Selecting the proper container for dispensing
  (glass or plastic, clear or opaque, cap liners)
- Predicting the shelf life of the drug.
- Anticipating drug excipients interactions
- Stabilization of the drugs against degradation

- In some cases a pharmacist may need to prepare stable compounded preparations from existing dosage form.
- It is the responsibility of the pharmacist via the information of the manufacture to instruct the patient in the proper storage and handling of the drug product.

- In general, the purpose of stability testing is to provide evidence on how the quality of a drug substance (active ingredient) or drug product (formulation) varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light.
- Stability testing permits the establishment of recommended storage conditions, retest periods, and shelf lives.
- Information on both drug substance (active ingredient) and drug product (formulation) are required by Food and Drug Administration (FDA) in reviewing application for new approval

Expiry date: refers to the date after which drug products can not be used since concentration of drug is lower than therapeutic concentration and some drug products' degradation are toxic and harmful to patients.

Note:

- Shelf-life should since manufacture date of product
- Maximum shelf life for such drug products as implants, injectables, tablets, capsules, soluble Powder is 5 years
- After opening of drug container, expiry date will be shorter due to effects of external factors

Examples:

- **Eye drops**: can be used for one month after opening the droppers
- **Syrups and suspension of antibiotics**: can be used for one week if stored in room temperature and for two weeks if stored at 4 ^{0}C
- **Tablets and capsules** remain stable in the package but after removal the expiry date will change
- **Ampoules**: must be used immediately
- **Vials** which are multidose are stable for 24 hours due to presence of preservatives

Five stabilities of drug must be considered::

1. Physical stability
2. Chemical stability
3. Microbiological stability
4. Therapeutic stability
5. Toxicological stability

Criteria for acceptable level of stability	
Types of stability	**Conditions to be maintained through out the shelf life of the drug product**
Physical	Such original physical properties as dissolution, suspendability, uniformity, palatability, and appearance should be retained
Chemical	Each active ingredient should retain its chemical integrity & labeled potency over limited periods
Microbiological	The product remain sterile and resistant to microbial growth. Antimicrobial agents present in the product retains its effectiveness over specified period
Therapeutic	Therapeutic effectiveness should remain unchanged
Toxicological	No significant increase in level of toxicity

Chemical stability is vital for:

- Selection of storage conditions
- Selection of proper containers & closures
- Anticipating potential interaction

Pharmaceutical degradation reactions:

- occur at definite rates
- chemical in nature

Note:

- Consideration of pharmaceutical chemical stability needs study of reaction order & reaction rate

- For a new drug, expiration date is usually set at the time when 10% of the initial (labeled) dose is degraded (i.e., 90% of the dose is still active) at room temperature.
- If A_0 is the initial amount of drug in the dosage form, we can determine the time required for a drug to decompose to 90% of its original activity

$$A_0 \rightarrow 0.9\,A_0$$

- Determining decomposition of drugs at room temperature for a year or more is both time consuming and expensive.
- Instead, companies have adopted an accelerated stability method that involves examination of the drug decomposition at higher temperatures and extrapolating the data to room temperature.

Note

The order of a reaction may change during the period of the study, especially at an elevated temperature. Thus, prediction of stability at room temperature based on results obtained from an elevated temperature study may not be always practical

Types of stability studies

1. Long term or Real time stability study
2. Accelerated or exaggerated stability study

During stability studies

- The length of the studies and the storage conditions should be sufficient to cover storage, shipment, and subsequent use
- Official storage conditions should be used

Official storage conditions	Temperature ranges [°C]
Cold	< 8
refrigerator	2-8
Freezer	-20 to -10
Cool	8 to 15
Room temperature	15 t0 30
Warm	30 to 40
Excessive heat	> 40

Objectives of accelerated stability tests

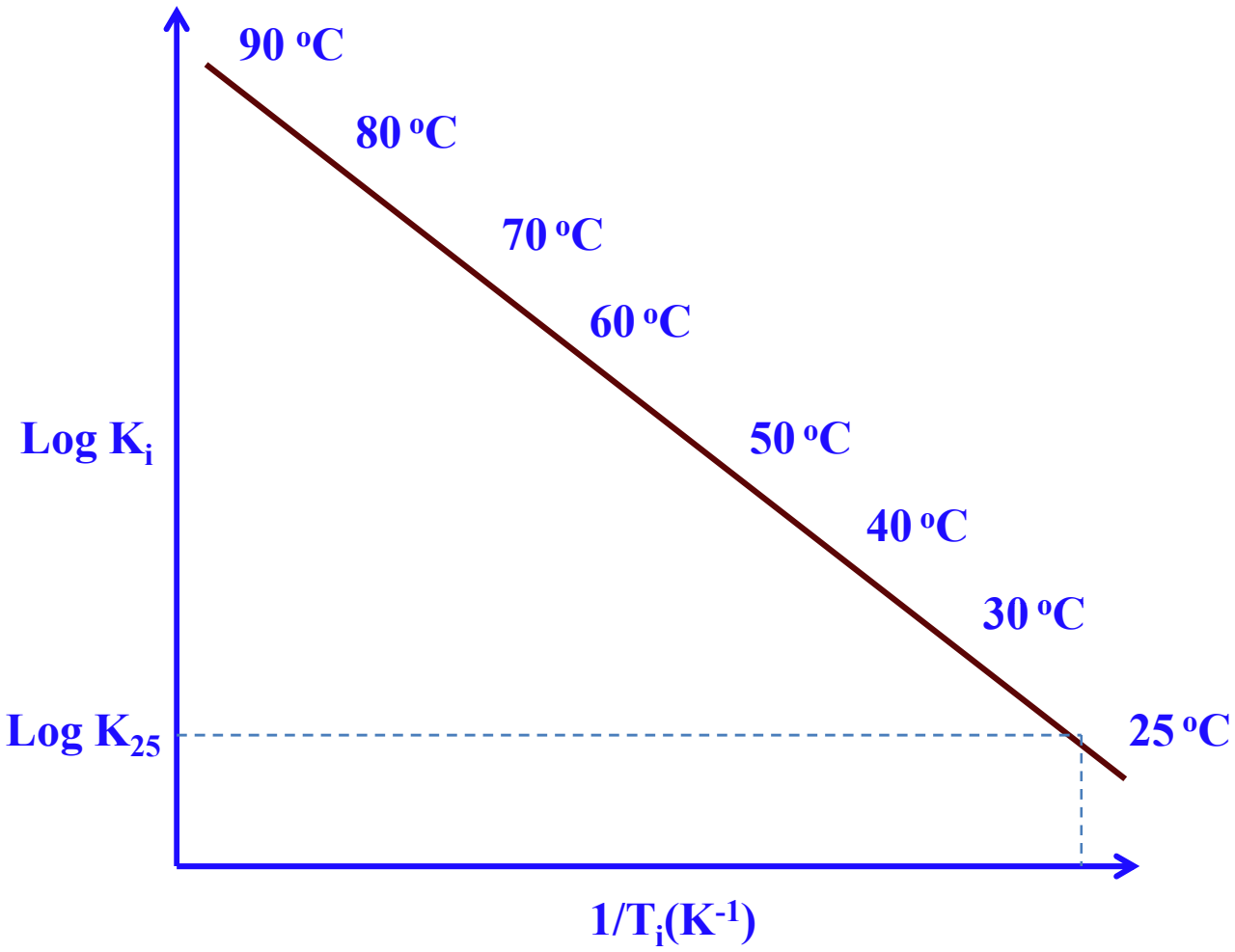
1. Quick evaluation of degradation in initial formulations of a product in selecting the best formulation from a series of possible choices.
2. Prediction of shelf life
3. Identification of a rapid quality control tool, which ensures that no unexpected change has occurred in the stored product

Accelerated stability testing protocols should define the followings

- The temperature and humidity for storage
- Time points and frequency of sampling
- The number of batches to be sampled
- The number of replicates within each batch
- A suitable light challenge
- Details of assay

Procedure for accelerated stability study

1. Measure the degradation rate constant (k_i) of the same formulation at several higher temperatures, T_i
2. Use an Arrhenius plot to determine the activation energy (Ea) and frequency factor (A).
3. Using data, calculate rate constant at room temp.
4. Alternatively, plot log k_i vs. $1/T_i$ according to the Arrhenius equation, and extrapolate k at room temperature from that plot.
5. Using k at room temp., determine the time required for a drug to decompose to 90% of its original amount.



Variation of log K_i with 1/T [Arrhenius plot]

6.9. Prediction of shelf-life & beyond use time

- Using k at room temp., determine the time required for a drug to decompose to 90% of its original amount as follow:

$Lnc_{25} = lnc_0 - K_1t$

C at 25 ^oC = 90% of Co = $0.9C_0$

$ln0.9C0 = lnc_0 - K_1t$

$t = [lnc_0 – ln0.9C0]\ K_1 = ln\ (C0/\ 0.9C0)\ K_1 = ln\ 1.11/\ K_1$

Therefore, shelf life of the drug at 25 ^oC is **$ln1.11/\ K_1$** unit of time

Unit 7.Radiopharmaceuticals

1. Introduction
2. Characteristics of radiopharmaceuticals
3. Labeling of Radiopharmaceuticals
4. Dispensing of Radiopharmaceuticals [RP]

Introduction

Radiopharmaceutical [RP]

- Pharmaceutical preparation containing radionuclide (radioactive isotopes) in the form of a simple salt or complex and intended for in vivo or *in vitro* use
- Exist as a solid, liquid or gas
- Chemical & physical identity of radiopharmaceutical is very important

Reason

RP is intended to target certain tissues, binding sites & /or biochemical path ways after administration

Radiopharmacy

- Branch of pharmacy that deals with the study of pharmaceutical, chemical, physical, biochemical, and biological aspects of radiopharmaceuticals
- Assures safe & efficacious use of RP
- Deals with :
  - Design, preparation and quality control of RPs
  - Relationship b/n physicochemical & biological properties & clinical applications of RP
  - Management, selection, storage, dispensing, & proper use of RP

Radioactivity

- Refers to spontaneous transformation of unstable nucleus to a more stable nucleus.
- Involves release of ionizing radiation in the form of α- & β- particles or electromagnetic radiation (γ -rays).
- **Alpha particles** are compound particles, consisting of two protons & two neutrons. Its range in air & tissues are 5 cm & 100 μm, respectively
- **Beta particles** exists as negative electron [Negatrons] & positive electron [positrons]. Both are identical in all aspects except their charges.
- Its penetration ranges in air & tissues are >3 m & up to 1 mm, respectively.

- β- & α- particles are locally destructive to tissues since they release large amounts of energy over a short distance [path]

Gamma rays

- Most penetrating of all types of radiation, with a penetration power of > 25 cm in tissues.
- Have no mass or charge
- Travel with the speed of light
- Useful as diagnostic radiopharmaceuticals; once the RP has distributed within the body, the photons can penetrate the tissues & be detected externally using specially designed imaging equipment

Radioactive Decay

Radionuclide stabilization process . **How ?**

- spontaneous fission
- α - particle emission
- β - particle emission
- positron emission
- γ – ray emission &/or
- electron capture

Note

1. In all decay processes the mass, energy, and charge of radionuclides must be conserved
2. Many nuclides can decay by a combination of any of the above - mentioned processes.

Radionuclides [Radioactive element]

Elements that emit radiation from unstable atoms

Application of radionuclides

- Basic research
- Sealed radiation sources
- Radiopharmaceuticals

- **Sealed radiation source [SRS]**

Sealed source is defined as radioactive material that is:

- Permanently sealed in a capsule or
- Closely bounded in a solid form.

Uses

- Therapeutic purpose
- Diagnostic purposes

Therapeutic uses of SRS

- Radiation therapy involves using ionizing radiation for treatment of diseases.
- The specialized field of using ionizing radiation for treatment of cancers is known as Radiation Oncology
- Therapeutic RP have a high target-to-background ratio
- Targeted radiotherapy involves the use of molecular carrier such as a receptor-avid compound or an antibody to deliver a radionuclide to cell populations
- Damage or kill cells by irradiation

Factors governing selection of radionuclide for a given therapeutic application

- Type of radiation
- Energy of radiation
- Tissue penetration range of radiation
- Physicochemical properties of radionuclide

Therapeutic uses of SRS

1. Teletherapy [External Beam Radiation Therapy]

- Radiation therapy that uses a machine outside of the body to deliver high-energy rays directed at the cancer or tumor
- Involves delivery of therapeutic radiation from a source that is placed away from the body.
- SRSs are externally beamed into cancerous tissue

External Beam Radiation Therapy machine

2. Brachytherapy

- Derived from ancient Greek words for short distance (brachios) and treatment (therapy)
- Refers to therapeutic use of encapsulated radionuclides or implanted SRS in the form of seeds, wires, or ribbons within or in proximity to a tumor for specified periods of time . It is an outpatient procedure used in the treatment of different kinds of cancer

❖ Thus, it is internal radiation treatment given by placing radioactive material directly into a tumor or close to the tumor

Forms of Brachytherapy based on placement site of SRS

Forms of Brachytherapy	placement site of SRS
1. Surface Mould Brachytherapy	on surface
2. Intra-cavitary Brachytherapy	within a body cavity such as Cervix, Vagina)
3. Intra-liuminal Brachytherapy	within lumen such as Oesophagus, Anal Canal
4. Endovascular Brachytherapy	within Blood Vessels
5. Interstitial Brachytherapy	Into organ or tissue such as Breast, Soft Tissue Sarcoma

Brachytherapy

- has been proven to be very effective and safe
- Provides a good alternative to surgical removal of prostate, breast and cervix
- Reduces risk of certain long-term side effects
- Currently, used to treat :
  - prostate cancer
  - cervical cancer
  - head and neck cancer
  - endometrial cancer
  - coronary artery disease

Benefits of brachytherapy

- Vary depending on the patient, their priorities and preferences
- Though as a minimally invasive treatment method, the benefits of avoiding surgery are universal
- Quicker recovery time, less time spent in the hospital
- Reduced risk of postoperative infections.
- Much lower incidence of impotence and incontinence than occurs with a radical prostatectomy
- Most men resume walking within a few hours of brachytherapy procedure and other normal activity within a few days

Radiopharmaceutical for diagnostic purpose

- Pharmacologically they are inactive
- Administered in small amount, hence never alter physiologic or pathophysiologic process to be measured
- Nature of emitted radiation should have ease of detection [i.e., to obtain an image or other diagnostic data]

The gamma camera. The patient is lying between detectors of double-headed system. To the right of the camera is a rack containing extra collimators. The technician is seated at the computer controlling data acquisition and image display.

- **Diagnostic radiopharmaceuticals** are used for getting information for diagnostic purposes via static imaging where the radiopharmaceutical is injected in the body (*in-vivo), allowed to localize in* the part of interest and then imaged to obtain data on the size, shape, location of tissues of interest.
- Some examples are imaging of such organs as liver, thyroid, kidneys to find their function or occurrence and extent of their damage, or tumours to find out their exact location and size

Half - life ($t_{1/2}$) of radionuclide

- Time required to reduce the initial activity of a radionuclide to one - half. That is, after one half - life, the activity of a radionuclide would be A /2, after two half - lives A /4, after three half lives A /8, and so on if 'A' is initial activity
- Relationship between decay constant ,λ and $t_{1/2}$ can be derived from general radioactive decay equation :

$$\mathbf{t_{1/2} = \ln 2 / \lambda = 0.693 / \lambda}$$

Examples

Radionuclide	**Half- time**
• 14C	5730 years
• 24Na	15 hours
• 81K	13 Seconds

Characteristics of radiopharmaceuticals

1. Can be as simple as a radioactive element such as 133 Xe, a simple salt such as 131 I- or a protein labeled with a radionuclide such as 99m Tc - labeled albumin or 90 Y - labeled monoclonal antibodies.
2. Contain minute amounts of active ingredients, with a radionuclide somehow linked to or being the active ingredient itself, with the main purpose of obtaining an image or a measure of their biodistribution

3. Show no measurable pharmacodynamic activity, as they are used in tracer quantities. Hence, there is no dose – response relationship in this case and thus differs significantly from conventional drugs.
4. Radiation is an inherent characteristic of all RPs .Hence, patients always receive an unavoidable radiation dose. In the case of therapeutic RPs, radiation is what produces the therapeutic effect.
5. Composition of radiopharmaceuticals is inconstant with time as radionuclide disintegrates. Very often, $\mathbf{t_{1/2}}$ of labelled molecule is so short that it must be freshly prepared just before its administration to patient.

6. RPs disappear from the organism by a combination of biological half-life & physical half-life

Note :50% reduction of radiopharmaceutical from the body is due to:

I. biological half-life [Tb]: such biological processes as metabolism, excretion,etc +

II. Physical half-life[Tp] : radioactive decay of the radionuclide

Effective half – life [Te]: Combination of both T-halves

$$\mathbf{Te = Tb.Tp/ Tb + Tp}$$

7. Diagnostic RPs should decay by γ emission, electron capture, or positron emission, and never emit α or even β particles.
8. Therapeutic radiopharmaceuticals should decay by α- or β- emission since the intended effect is radiation damage to specific cells

Labeling Radiopharmaceuticals

- Name of the product
- Batch Number
- Manufacturing date
- Shelf- life [EXP. Date]
- Standard radiation symbol
- Caution: radioactive material
- Storage conditions
- Address of manufacturer

The ISO 361 radiation symbol

Dispensing of Radiopharmaceuticals [RP]

- RPs are not directly dispensed to patients
- RPs are provided directly to trained health care professionals at the health facilities.
- Administered to patient by health care professionals
- They are dispensed in a unit doses.
- Dispensing of RP requires considerations of :
  I. Patient factors such as age, weight, surface area
  II. Radioactive decay to accommodate the time from manufacture to administration.

Unit 8: Incompatibility

Introduction

- Incompatibility occurs when one drug is mixed with other drugs or excipients, producing a product unsuitable for administration
- Incompatibility among mixed items is manifested by changes in physical, chemical & /or therapeutic qualities which in turn influence the safety, efficacy & appearance of a medicine
- Existence of incompatibility is anticipated by pharmacist on the basis of his/her pharmaceutical, chemical & pharmacological knowledge

Types of incompatibility

- Physical incompatibility
- Chemical incompatibility
- Therapeutic incompatibility

Physical incompatibility

- Caused by immiscibility, insolubility, liquefaction

Physical incompatibility due to immiscibility

- **Mixing** oils with water leads to demixing
  - ➢alleviated by using effective emulgent
- Addition of conc. hydroalcoholic solutions of volatile oils [eg: spirits] & conc.water which are used as adjuncts [eg: flavoring agents] in aqueous preparations.
  - ➢Separation & formation of large oily globules
- Addition of high concentration of electrolytes to a saturated aqueous solution of volatile oil

➢ Salting out of oil [soln: use suspending & emulsifying agents]

Physical incompatibility due to insolubility

- Preparation containing such indifussible substance as chalk, aromatic chalk powder, or calamine & zinc oxide lotion suffer from insolubility

  ➢**Use suspending agents**

- Poorly wettable drugs such as corticosteroids , sulphur, & some antibiotics are insoluble in water

  ➢**Use appropriate wetting agents**

- Using excessive SAAs cause deflocculating [breaking down of solid into individual particles] of solid powder thus triggering formation of clay [very tightly packed sediment].

  ➢**Employ optimal quantity of SAAs**

Physical incompatibility due to liquefaction

Liquefaction intervenes with dispensing of components as a solid mixture

Preparation containing powder solid pair of camphor, thymol, salol, phenol, menthol & chloral hydrate forms eutectic mixture with m.p. below room temperature

- Forms liquid eutectic mixture

Remedy

Triturate liquid eutectic with enough efficient adsorbent substance that has high m.p. & large specific surface area [eg: light kaolin or light $MgCO_3$] to form a free flowing product

Chemical incompatibility:

- Mediated by pH change, double decomposition reaction or complex formation between the ingredients of a preparation.
- If the product of the interaction is harmless then the incompatibility can be adjusted or tolerated
- Causes of chemical incompatibility can be:
  - Hydrolysis
  - Oxidation
  - Photolysis
  - Trace metal catalysis
  - Chelation

Hydrolysis [Solvolysis] triggered chemical incompatibility:

- Drug molecules containing ester, amide, lactone, lactam, imide or carbamate bond are liable to hydrolytic degradation.
- Hydrolytic reactions involve nucleophilic attack of labile bonds
- Level of susceptibility of drug in solution to hydrolysis

Lactam > ester > amide > imide

Examples

- Penicillin & cephalosporin have β-lactam ring
- ASA has ester bond

pH triggered chemical incompatibility

- Degradation of most drugs is catalyzed by extremes of pH, i.e. high $[H_3O^+]$ & $[OH^-]$
- Many drugs are most stable between pH 4 & 8

Oxidation caused chemical incompatibility

- Involves removal of electropositive atom, radical or electron, or addition of an electronegative atom or radical
- Catalyzed by light, trace metals, oxygen and oxidizing agents
- Oxidative degradation involves:
  - Autoxidation: Uncatalyzed reaction but proceeds quite slowly under influence of O_2

or

  - Chain reactions :initiation, propagation & termination

Initiation

Factors that trigger oxidation reaction include

Free radicals formed from organic compounds by the action of light, heat or transition metals such as copper and iron which are present in trace amounts in almost every buffer

Propagation stage

Involves combination of molecular oxygen with free radical 'RO$^{-\cdot}$ to form a peroxy radical 'ROO$^{-\cdot}$, which then removes H from a molecule of the organic compound to form a hydroperoxide, ROOH, and in so doing creates a new free radical

Termination stage

Involves destruction of free radicals either by **inhibitors** or by side-reactions so as to eventually break the reaction chain

Simplified oxidation scheme involving a chain process

Initiation:

$$X\bullet + RH \rightarrow R\bullet + XH$$

Propagation:

$$O_2 + R\bullet \rightarrow ROO\bullet$$

$$ROO\bullet + RH \rightarrow ROOH + R\bullet$$

Termination:

$$ROO\bullet + ROO\bullet \rightarrow \text{stable product}$$

$$ROO\bullet + R\bullet \rightarrow \text{stable product}$$

$$R\bullet + R\bullet \rightarrow \text{stable product}$$

Examples of drugs susceptible to oxidation degradation

- Steroids and sterols [due to double bond]
- Polyunsaturated fatty acids [vegetable oil]
- Simvastatin[cholesterol-lowering agent]
- Amphotericin B

Precautions to be taken to minimize product oxidation during manufacturing & storage

- Replace oxygen in pharmaceutical containers with nitrogen or carbon dioxide
- Avoid contact of oxidizable drug with heavy-metal ions such as iron, cobalt or nickel as they catalyze oxidation reaction
- Store at reduced temperature
- Incorporate antioxidants in the formulation

Photochemical decomposition [Photolysis]:

- Degradation of drug products when exposed to light during storage &/or use of the product
- Causes loss of potency of the drug
- Manifested by discoloration or formation of a precipitate.

Examples

Hydrocortisone, prednisolone, riboflavin, ascorbic acid and folic acid, etc

Remedy

- ❖ Use amber containers
- ❖ Store in the dark
- ❖ Coat tablets with a polymer film containing ultraviolet absorbers

Therapeutic incompatibility[TI]

Undesirable pharmacological interaction between two or more ingredients

Consequences of TI

- Potentiating therapeutic effects
- Destruction of therapeutic effectiveness
- Toxicity

Types of therapeutic incompatibility

1. Pharmacodynamic incompatibility
2. Pharmacokinetic incompatibility

Pharmacodynamic incompatibility

- Occurs when two drugs act on same pharmacological receptors, sites of action or physiologic system to induce similar or antagonistic effects

Examples:

- Hypnotics & antianxiolytics both have CNS depressant action
- Probencid potentiate effects of penicillin
- Diuretics potentiate effects of digitalis because diuretics cause depletion of potassium

Pharmacokinetic interactions

Occurs when one drug alters absorption, distribution, metabolism & /or elimination of another drug

1. Interactions due to altered drug absorption

Example **:** TTC + divalent atom containing medicines

2. Interactions due to altered drug distributions **[plasma protein displacement]**

Example:

- Displacement of warfarin by clofibrate = bleedings
- Displacement of Tolbutamide by salicylates precipitates hypoglycemic effects of the former.

3. Interactions due to altered drug metabolisms:

- Induction & inhibition of P-450 hepatic microsomal enzymes gradually increases & decreases, respectively clearance of other drugs that are metabolized by these groups of enzymes

Examples:

- Metronidazole retard metabolism of warfarin
- Barbiturate & phenytoin accelerate metabolism of oral anticoagulants
- CAF reduces metabolism of Tolbutamide & phenytoin

4.Interactions due to altered drug elimination [excretion]

- Change in urinary pH will alter rate of urinary drug reabsorption or excretion
- Probenicid inhibit tubular secretion of penicillin, indomethacin
- **Acidified urine** facilitate elimination of alkaline drugs but enhance retention of acidic drugs

Example:NH4 Cl + Sulphonamides[acidic drug] ??

NaHCo3 + Sulphonamides…. ???

- **Alkalinized urine** accelerate excretion of acidic drugs but increase retention of basic drugs

ASA + $NaHCO_3$ leads to ?

Summary of causes of interactions and incompatibilities

- Changes in pH leading to precipitation of the drug
- Change of solvent characteristics on dilution, which may also cause precipitation
- Cation–anion interactions forming insoluble complexes
- Influence of salts on decreasing or increasing solubility, respectively *salting-out* and *salting-in*
- Chelation : where chelator binds with a metal ion to form a complex

- Ion exchange interactions[ionized drugs interact with oppositely charged resins]
- Adsorption to excipients & / or containers causing drug loss
- Interactions of drug with plastics containers
- Binding to plasma proteins through which the free plasma concentration of drugs is reduced
- Displacement from plasma protein causing toxicity of displaced drug

Unit 9: Modified Release Preparations

9.1. Introduction

9.2. Types of modified release preparations

9.3. Mechanisms of drug release

9.4. Kinetics of drug release

9.5. Formulation consideration

9.1. Introduction

- A drug is rarely administered to human being as a pure chemical compound but as a dosage form , a drug product or a delivery system suitable for administration
- Almost anything done to dosage form may alter drug availability (the rate and the amount) to desired place in the body

- For many disease states, the ideal dosage regimen should attain acceptable therapeutic concentration of drug at the site(s) of action immediately following administration and is then maintained constant for the desired duration of therapy

- Administration of right dose size at the right dosage regimen achieves therapeutic 'steady-state' plasma drug concentrations promptly and then maintained by administering repetitive doses of conventional peroral dosage forms
- Administration of medicines by the oral route is the most straightforward option for patients. It is the most commonly used route, with more than 70% of all medicines being delivered in this way.
- Oral medicines are easy to administer, improve patient compliance and are cheaper than some of the alternatives (e.g. injections).

- ‘Conventional peroral oral dosage form is designed to release rapidly complete dose of drug immediately following administration
- In addition, the released drug is assumed to be in a form that is therapeutically active and immediately available for absorption
- Most medicines given by oral route offer ‘immediate-release’ or ‘conventional’ drug delivery to reveal rapid onset of action.
- However, some situations need slow drug release profile & long lasting effects which in turn needs modification of drug release pattern.

Limitations of ‘Conventional' peroral oral dosage form

1. Drug concentration in plasma & at the site(s) of action fluctuates over successive dosing intervals, even after achieving steady-state' condition. Hence it is not possible to maintain a therapeutic concentration of drug that remains constant at the site(s) of action for the duration of treatment. At best, the mean value of the maximum and minimum plasma concentrations associated with each successive dose remains constant for the period of drug treatment

2. Inevitable fluctuations of steady-state concentrations of drug in plasma, and hence at the site(s) of action leads to a patient being over- or under-medicated for periods of time
3. Drugs having short biological half-lives require frequent dosing to maintain steady state plasma concentrations within therapeutic range. For such drugs the maintenance of therapeutic plasma concentrations is particularly susceptible to consequence of forgotten doses & overnight no-dose period
4. Therapeutic inefficiency or failure due to lack of patient compliance is associated with regimens requiring frequent administration of conventional dosage forms

Thus, modified release dosage forms are required.

What are modified release dosage forms?

- They are drug products designed to alter the time and rate of release of bioactive agent (drug substance)
- They refer to manipulation or modification of drug release from a dosage form (e.g. tablet, pellet, capsule) with the aim of delivering active pharmaceutical ingredients (API) at desired rates, pre-defined time points, or specific sites in the git
- Peroral dosage forms that continuously release drugs at controlled rates to provide periods of prolonged therapeutic action following single dose administration
- Achieves certain therapeutic or convenience objectives that conventional dosage forms never offer

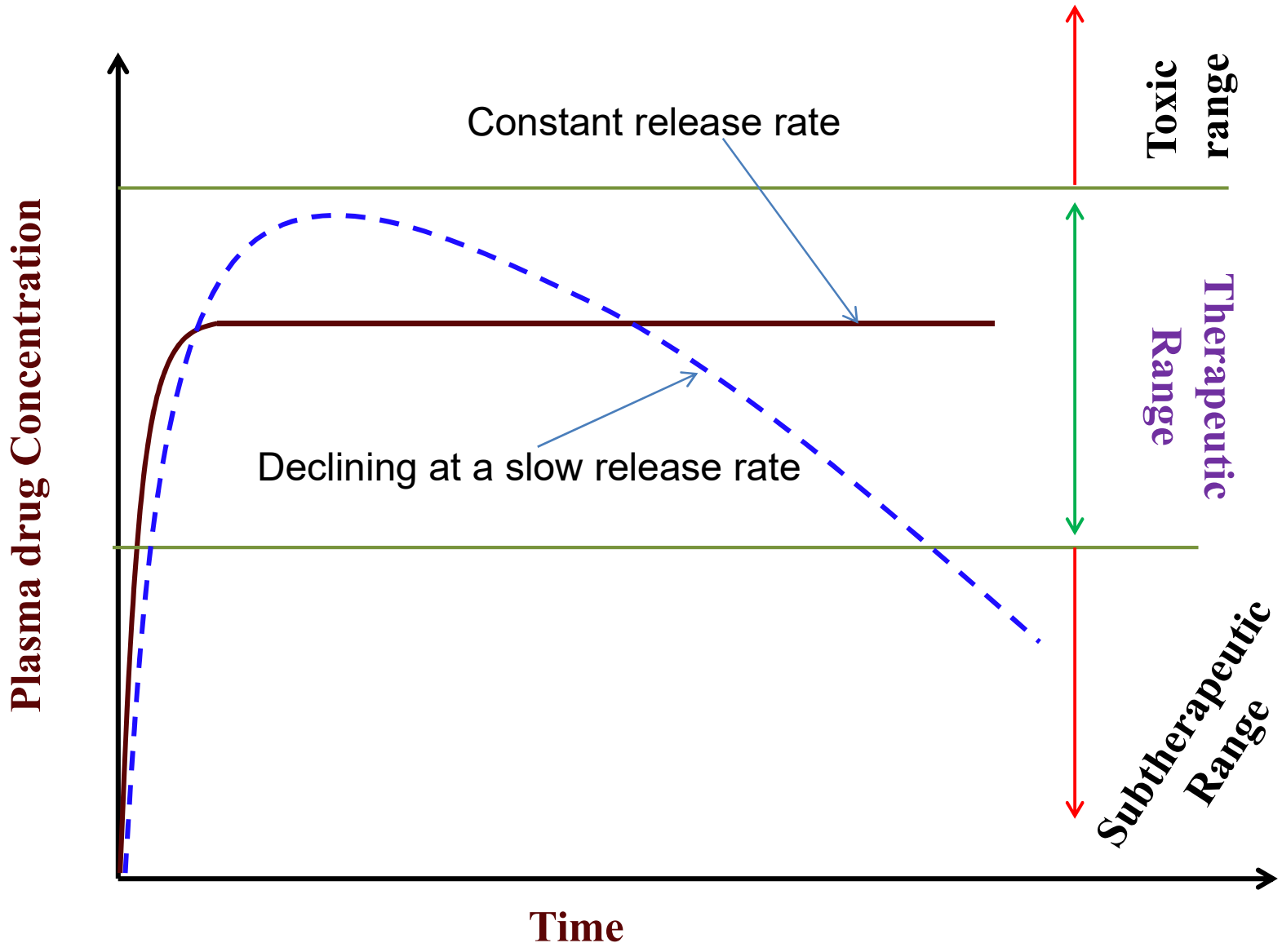
Objectives of modified release dosage forms

Providing either prompt achievement of a plasma concentration of drug that:

- remains essentially constant at a value within the therapeutic range of the drug for a satisfactorily prolonged period of time

or

- although not remaining constant, declines at such a slow rate that the plasma concentration remains within the therapeutic range for a satisfactorily prolonged period of time



Serum drug conc. vs. time curves of modified release peroral dosage forms

9.2: Types of modified release dosage forms

A. Delayed release dosage forms
B. Controlled [Prolonged /Extended] release dosage forms
C. Sustained release dosage forms
D. Targeted dosage forms

A. Delayed release or Gastro-resistant dosage forms:

- Repetitive, intermittent dosings of a drug occur from one or more immediate-release units added into a single d.f.

Types of delayed-release dosage forms

1. Repeat-action (release of two doses successively)
2. Enteric coated tablets/capsules : Timed release is achieved by a polymer barrier coating to release drug in the small intestine
3. Modified enteric coated tablets : Additional drug is applied over enteric coat and is released in the stomach, while the enteric coated remainder is released further down the small intestine

B. Controlled (Prolonged or Extended) release d.f

Release drug slowly to maintain constant plasma drug concentration over prolonged duration of therapy, but onset of action is delayed

1. Releases bioactive agent (drug) over extended period of time
2. Avoids undesirable saw tooth features of plasma conc. vs. time profiles of conventional drug products
3. Dosage form controls release rate of incorporated drugs & maintaining constant drug concentrations at the biophase: target tissue or cells, i.e, drug release rate is determined by design of the system & physicochemical properties of drug

4. Drug release rate is independent of external factors [microenvironment] in which the dosage form is placed
5. Design of controlled release dosage forms is based on the philosophy that when level & time of availability of the drug to the target tissue are optimized, optimum biological response occurs
6. Since release-rate control complements drug molecular structure in determining both selectivity and duration of action, it is believed that controlled-release drug-delivery systems permit more accurate, effective, reproducible & predictable drug administration

C. Sustained release dosage forms

Characterized by an initial release of drug sufficient to provide a therapeutic dose soon after administration, and then a gradual release over an extended period

Differences b/n repeat-action & sustained release preparations

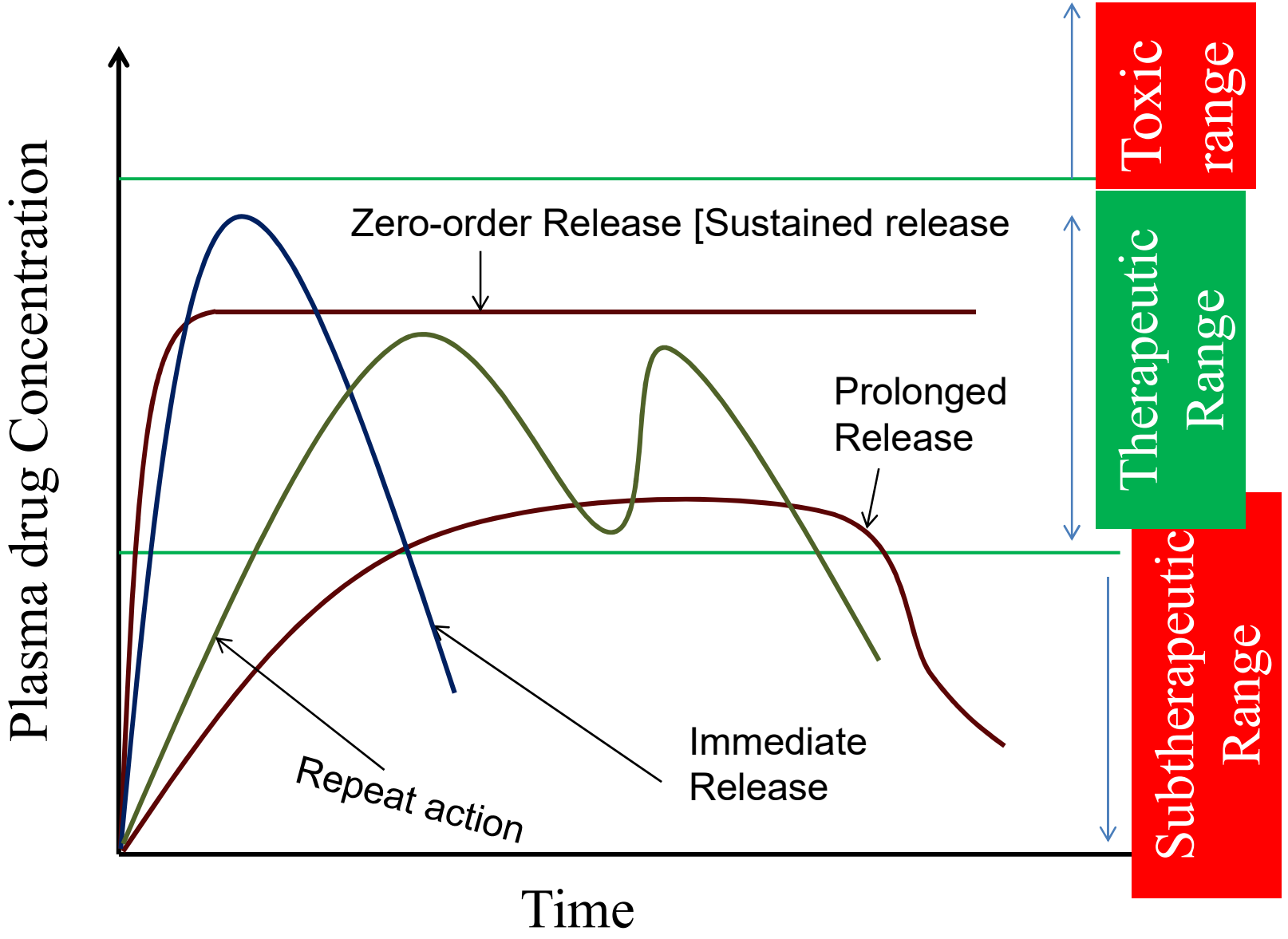
1. Repeat-action product does not release drug in a slow controlled manner, hence never give a plasma concentration-time curve resembling that of a sustained-release product
2. A repeat-action tablet usually contains two or three doses of drug, the first being released immediately to provide a rapid onset of action
3. Release of enteric coated second dose is delayed, until breached by intestinal fluids
4. AUC obtained from repeat-action preparation exhibits 'peak & valley' profile similar to intermittently administered conventional dosage forms

D. Targeted dosage forms

- Two types of targeted dosage forms are commonly described:
  - ➢Site specific targeting
  - ➢ Receptor targeting
- In site-specific targeting, drug release is at diseased organ or site of absorption
- In receptor targeting, drug release is at the receptor for the drug action

Note

- All the dosage forms described above can be grouped under the generalized term Controlled Drug Delivery
- CDD is now a generalized term that encompasses any system that is capable of spatial placement and temporal delivery of a drug
- In spatial placement, the drug is targeted to a specific organ or tissue (this includes targeted dosage forms)
- In temporal delivery, the rate of drug delivery to the target tissue is controlled (eg.: delayed and controlled release dosage forms plus pulsatile or modulated drug delivery systems because the rate of delivery is controlled based on human physiological need)



Serum drug concentration vs. time curves of various oral dosage forms

Advantages of controlled release drug delivery systems

1. Increase efficacy by maintaining constant plasma drug level in the therapeutic window range for an extended period of time
2. Reduce dosing frequency
3. Eliminate drug accumulation in the body, thereby minimizing untoward effects
4. Increases patient compliance
5. Minimizes cost of treatment for chronic diseases

Drawbacks of controlled release dosage forms

- Should patient suffer from adverse drug reaction or become accidentally intoxicated, removal of drug from the system may be difficult, if not impossible
- When orally administered it may yield erratic or variable drug absorption owing to interactions with contents of git and changes in gastrointestinal motility resulting in drug ineffectiveness
- Dose dumping from failure of controlled release dosage forms resulting in potentially adverse plasma drug levels

Note

- Dose dumping refers to release of more than the usual fraction of drug or release of drug at a greater rate than the customary amount of drug per dosing interval
- CRD forms are particularly prone to dose dumping if not properly designed and fabricated because they usually contain the equivalent of two or more drug doses present in a conventional dosage form.

  For example delayed and enteric coated dosage forms: If poorly formulated, the enteric coating may be dissolved in the stomach, resulting in premature release of the drug with the concomitant irritation of gastric mucosa
- Moreover, if the coating is poorly done, the enteric coating may not dissolve at the proper site along the gastrointestinal tract. Thus, the drug may not be available for absorption.

9.3. Mechanisms of drug release

Two basic mechanisms controlling drug release are:

- ❖ Dissolution of the active drug component
- ❖ Diffusion of dissolved or solubilized drug molecules

Four independently, simultaneously or consecutively operating processes are involved within the context of aforementioned mechanisms:

1. Hydrating of the device (swelling of the hydrocolloid or dissolution of the channelling agent)
2. Diffusion of water into the device
3. Dissolution of the drug
4. Diffusion of dissolved drug out of the device

9.4. Kinetics of drug release for ideal MR peroral dosage form

- MR peroral dosage form consists of two portions
  - ❖Initial priming/loading dose, Ld
  - ❖ Maintenance or sustained dose, Md.

- Drug Ld is released rapidly into the gi. fluids immediately following administration of MR d.f.
- Released dose is absorbed into body compartment rapidly following a first-order kinetic process i.e. characterized by apparent absorption rate constant, *K'a*

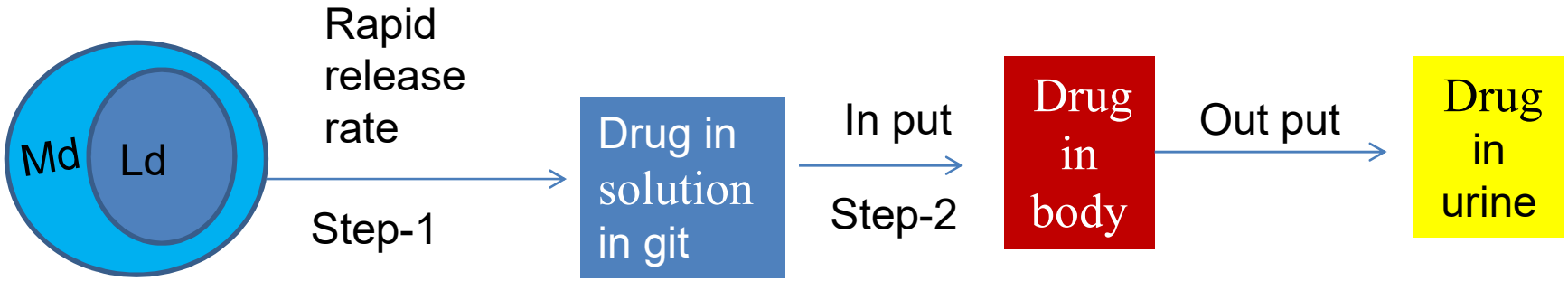
Objectives of Ld: Rapid attainment of therapeutic plasma drug conc. that provides rapid onset of action

- The portion Md of drug remaining in the dosage form is released by zero-order kinetics, i.e. zero-order rate constant ko.

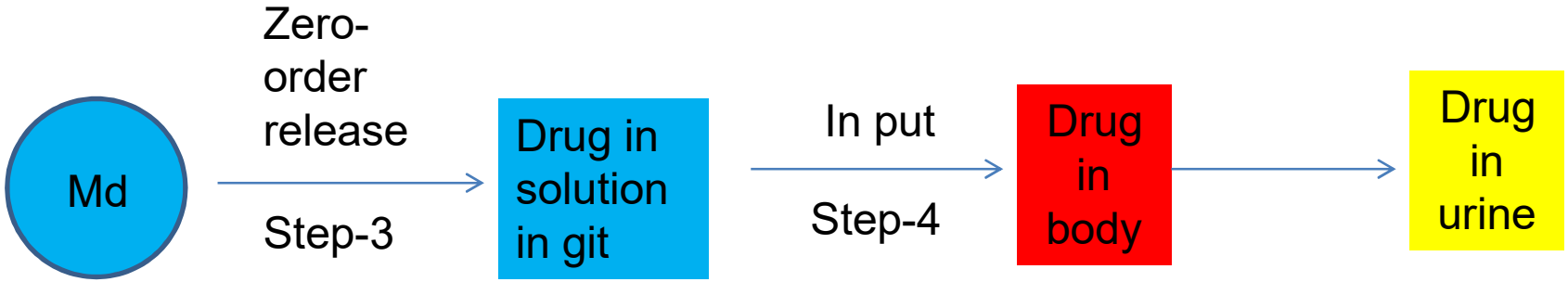
Thus, the rate of release of drug from maintenance dose remain constant independent of amount of drug remaining in the dosage form at any given time

Schematic presentation on kinetics of drug release from MR

A. Release & absorption of initial priming dose [Ld]



B. Release & absorption of maintenance dose [Md]



Conditions that must be fulfilled to ensure therapeutic concentration of drug in the body remains constant

1. MR dosage form must have loading and maintenance doses
2. Drug from Ld must be immediately released and hence absorbed by first order absorption rate constant
3. Zero-order release rate of drug from the Md must be rate determining wrt. the rate at which released drug is subsequently absorbed into the body. Kinetics of absorption of the Md will thus be characterized by the same zero-order release rate constant, *ko*
4. The rate at which Md is released from dosage form, & hence the rate of absorption (input) of drug into the body, must be equal to the rate of drug output from the body when the conc. of drug in the body is at the required therapeutic value

9.5. Formulation consideration

Main types of oral modified release delivery systems based on pattern of drug release:

- ❖ Monolithic or matrix systems
- ❖ Reservoir or membrane-controlled systems
- ❖ Osmotic pump systems

Alternative classification of oral MR delivery systems based on nature of excipients used

- Inert delivery systems
- Lipid delivery systems
- Hydrophilic delivery systems

Types of excipients	Examples of excipients	Types of delivery systems
Inert excipients	Dibasic calcium phosphate Ethyl cellulose Methacrylate copolymer Polyamide Polyethylene Polyvinyl acetate	**Inert delivery system**
Lipid excipients	Carnauba wax Cetyl alcohol Hydrogenated vegetable oils Microcrystalline waxes Mono- and triglycerides PEG monostearate PEG	**Lipid delivery system**
Hydrophilic excipients	Alginates Carbopol Gelatin Hydroxypropylcellulose HPMC Methylcellulose	**Hydrophilic delivery system**

Note:

Basic principles governing all aforementioned systems

1. Osmosis occurs from surrounding body fluids into the delivery system following water concentration gradient
2. Drug in a solution form diffuses out from the delivery system into surrounding body fluid following drug concentration gradient

Components of a modified-release delivery system

1. Active drug
2. Release-controlling agents [matrix & membrane formers]
3. Matrix or membrane modifier[channelling agents for wax matrices and solubilizers & wicking agents for hydrophilic matrices]
4. Solubilizers, pH and/or density modifiers
5. Lubricant and flow aid [magnesium stearate, stearic acid, hydrogenated vegetable oil, sodium stearyl ,talc, colloidal silicon dioxide]
6. Supplementary coatings to extend lag time, further reduce drug release

Monolithic matrix delivery systems [2 types]

1. Hydrophilic colloid matrices

- Made of drug particles dispersed in a soluble matrix, such that drug is released as the matrix dissolves or swells and dissolves
- The slow dissolution of the matrix provides sustained release pattern of the drugs dispersed in a soluble matrix
- Excipients used to provide a soluble matrix often are those used to make soluble film coatings
- Alternatively, slowly dissolving fats and waxes can be used.

2. Lipid matrices & insoluble polymer matrices DS

- The drug particles dispersed in an insoluble matrix, is released as solvent enters the matrix and dissolves the drug particles. **How?**
- Drug release from insoluble matrices follows penetration of fluid, followed by dissolution of the drug particles and diffusion through fluid filled pores This type of delivery system is unsuitable for insoluble or poorly aqueous soluble drug
- Excipients used in the preparation of insoluble matrices include hydrophobic polymers, such as polyvinyl acetate, ethylcellulose and some waxes

Reservoir or membrane-controlled drug systems

- Drug release rate is controlled by **insoluble** but **permeable** polymeric membrane
- A drug reservoir consisting of drug that should not diffuse in the solid state , e.g. a tablet or multi-particulate pellet, is coated with a membrane.
- Aqueous medium such as GI- fluid diffusing into the system and forming a continuous phase through the membrane initiates drug diffusion and release

Components of a membrane-controlled system

A. Core

- ❖ Active drug
- ❖ Filler or substrate [lactose, microcrystalline cellulose, dextrose, sucrose and polyols (mannitol, sorbitol]
- ❖ Solubilizer such as buffers, surfactants,polyols & PEGs
- ❖ Lubricant/glidant such as magnesium or calcium stearate

B. Coating

- ➢ Membrane polymer
- ➢ Plasticizer
- ➢ Membrane modifier or channelling agent such as sodium chloride, sugars and Polyols
- ➢ Colour/opacifier

Membrane polymers

- Critical part of the formulation as it controls drug release
- Nature of polymeric material governs drug release rate from reservoir devices.
- It should remain intact for the period of drug release, i.e. without swelling or subsequent erosion, as seen in hydrophilic matrices
- Polymer with high glass transition temperature & high degree of crystallinity have slow drug release rate
- Typical polymers used include **ethyl cellulose**, **acrylic copolymers**

Methods to circumvent very low permeability of the coating polymer

1. Incorporating pore formers or water-soluble additives into the polymer coating

- In the gastrointestinal fluid, the pore-formers in the polymer coating dissolve making porous coating polymer through which lipophilic and hydrophilic drugs can easily diffuse out
- Drug release rate is a function of the total concentration of (both dissociated & undissociated) drug within the core

2. **Incorporation of plasticizers** into coating polymer

- They lower glass-transition temperature [Tg] or increase uptake of fluids into the polymer coating
- Based on their solubility level, they may remain in the coating or be eluted to form micro/macr-pores

3. **Employing copolymers** that lower Tg & improve uptake of aqueous fluid since their permeability is adequate without incorporation of any additives

   Example: Tg of such copolymers as methyl methacrylate & ethacrylate is about 5 ^{o}C; hence absorb substantially more water at 37 ^{o}C than do homopolymers such as polymethylmethacrylate

- **The glass transition temperature** is the temperature range where the polymer substrate changes from a rigid glassy material to a soft (not melted) material, and is usually measured in terms of the stiffness, or modulus
- Glass transition temperature is the temperature, below which the physical properties of plastics change to those of a glassy or crystalline state. Above T_g they behave like rubbery materials. Below the T_g a plastic's molecules have relatively little mobility

Note

- In reservoir system, the polymer membrane is only at the surface of the system, whereas in the matrix system, the polymer is throughout the whole system
- In both cases hydration of the polymer is the step that allows the drug to diffuse
- Unlike hydrophilic matrix systems, membrane polymer neither swell on hydration to form a hydrocolloid matrix nor erode
- With the classic membrane system there are two diffusion processes: 'water in' followed by 'drug out'.

Osmotic pump systems[OPS]

- The tablet core consists of osmotically active drug or excipient
- The tablet core that is coated with a semipermeable membrane allows water ingress into the core, to dissolve or suspend the loaded drug
- As the core dissolves/suspends, a hydrostatic pressure builds up and forces (pumps) drug solution (or suspension) through a hole drilled in the coating
- Drug release rate from OPS is governed by the rate at which water ingresses via the membrane, and how quickly the drug solution (or suspension) passes out of the hole

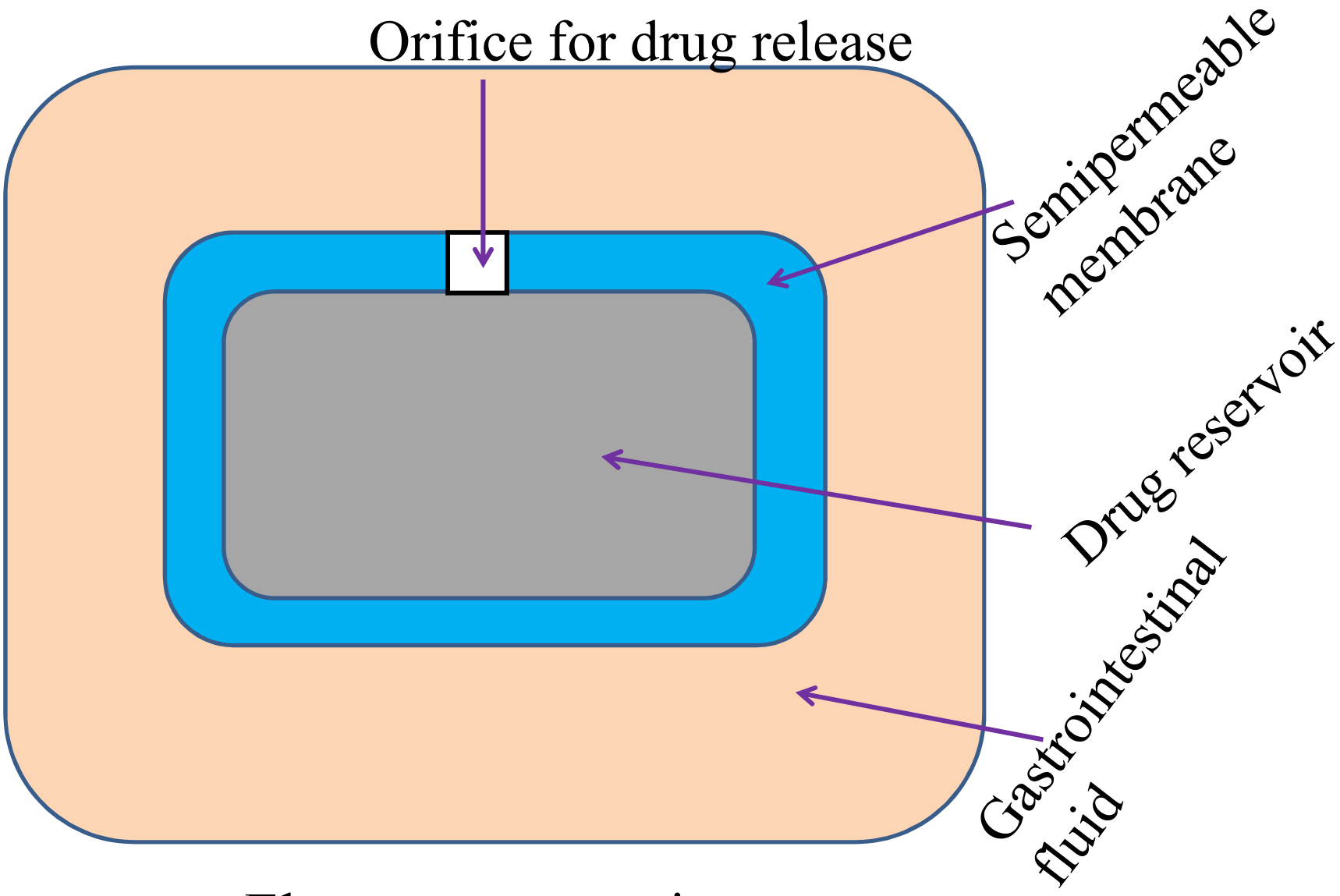
Components of osmotic pump systems

A. Core

- Consists of active drug, a filler or substrate, a viscosity modifier, solubilizer) and lubricant/glidant.

B. Coating

- Coatings contain a membrane polymer, a plasticizer, a (membrane modifier) and (colour/ opacifier).



Elementary osmotic pump

Essential difference between osmotic pump and 'classic' membrane-controlled system

- For osmotic pump only one diffusion process is required ('water in').
- For 'classic' membrane-controlled system two processes are key: water in, drug out

Unit 10: Cosmetics ……5 hrs

1.Introduction

2.Hair cosmetics

3.Skin cosmetics

4.Deodorants & antiperspirants

5.Oral care products

6.Nail products

7.Eye cosmetics

8.Lip products

End of the course

I wish you green events all the time

Bear in mind:

A man with one watch knows what time it is

However

A man with two watches never knows

Thank you